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OPHTHALMOLOGY

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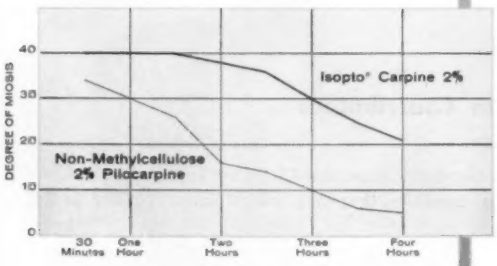

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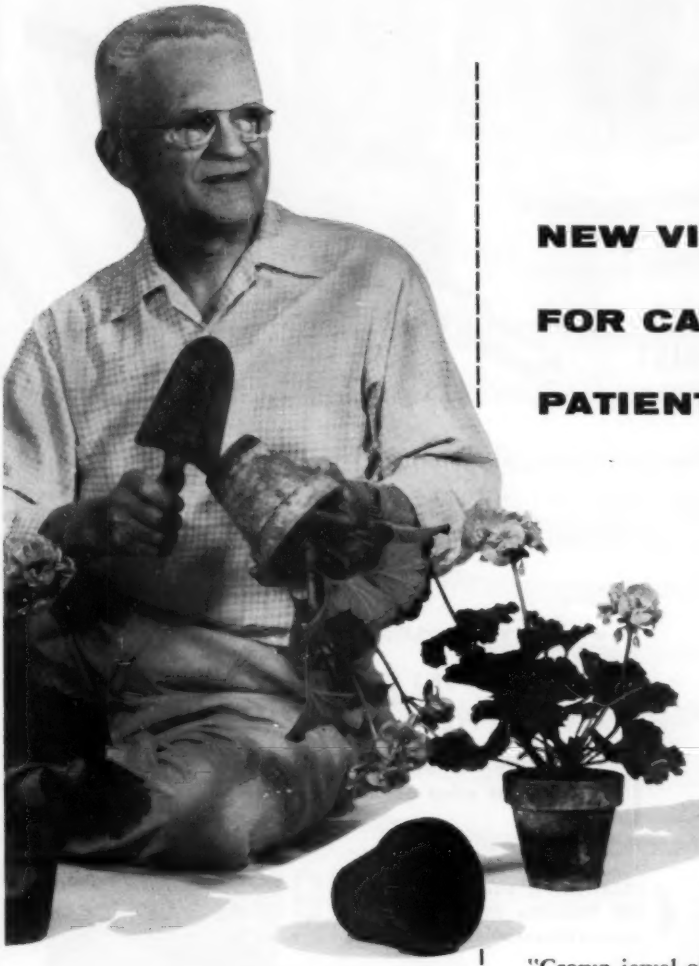

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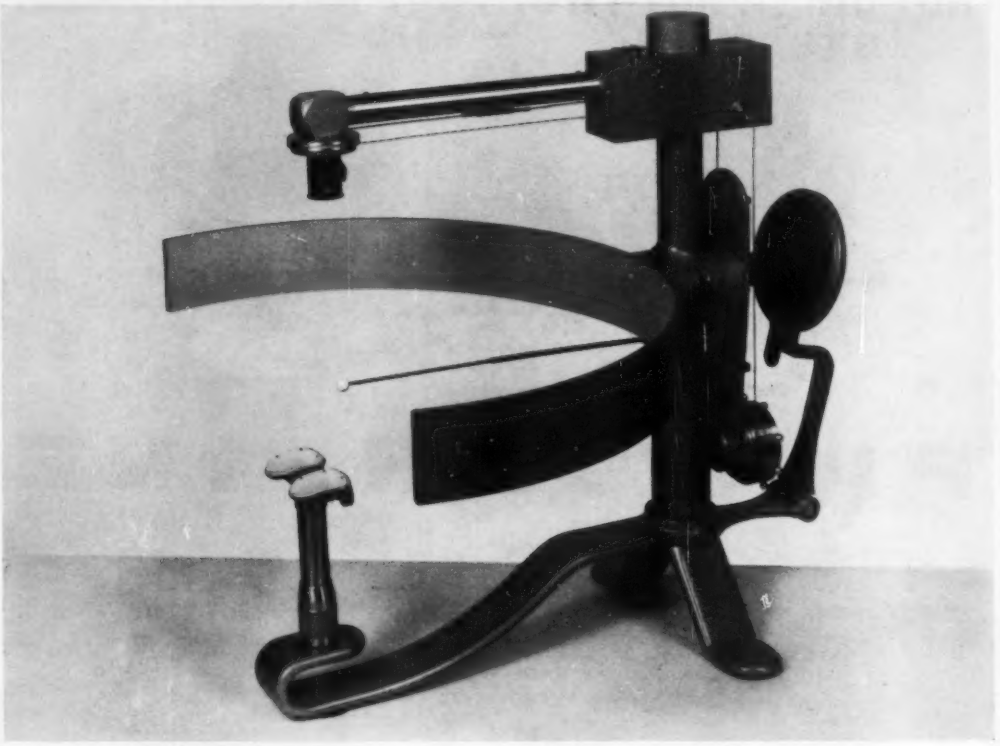

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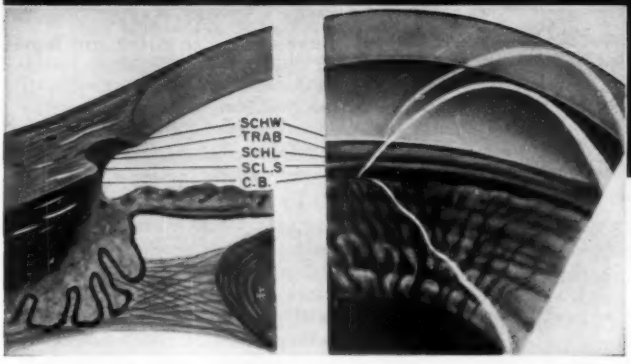

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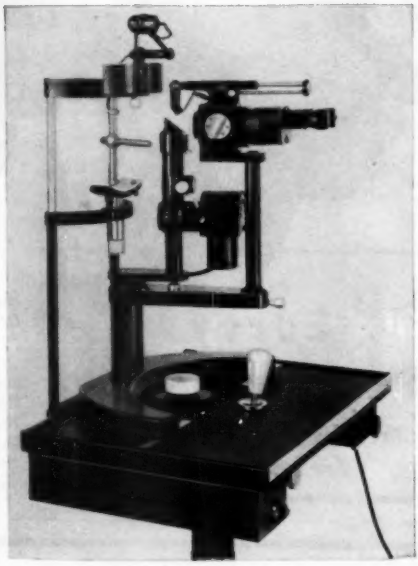

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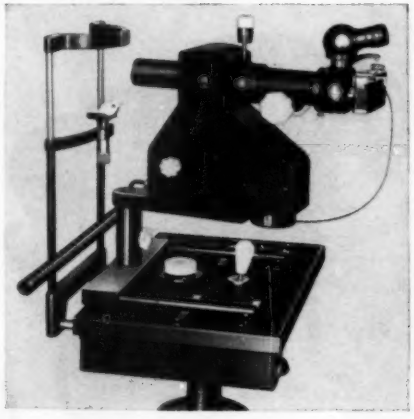

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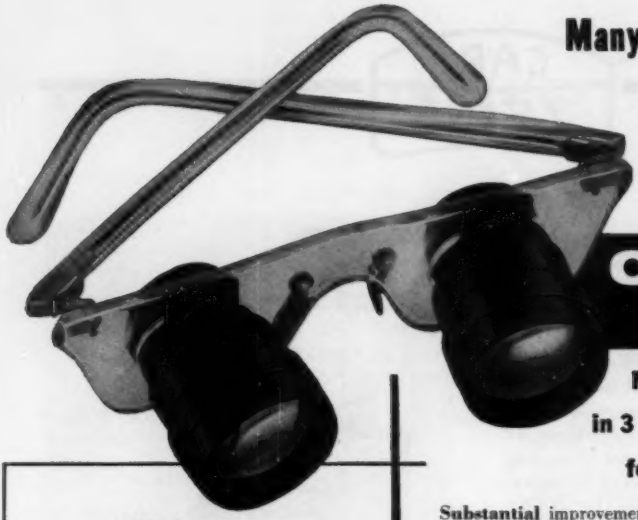

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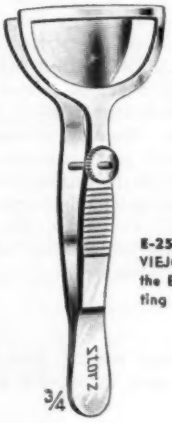

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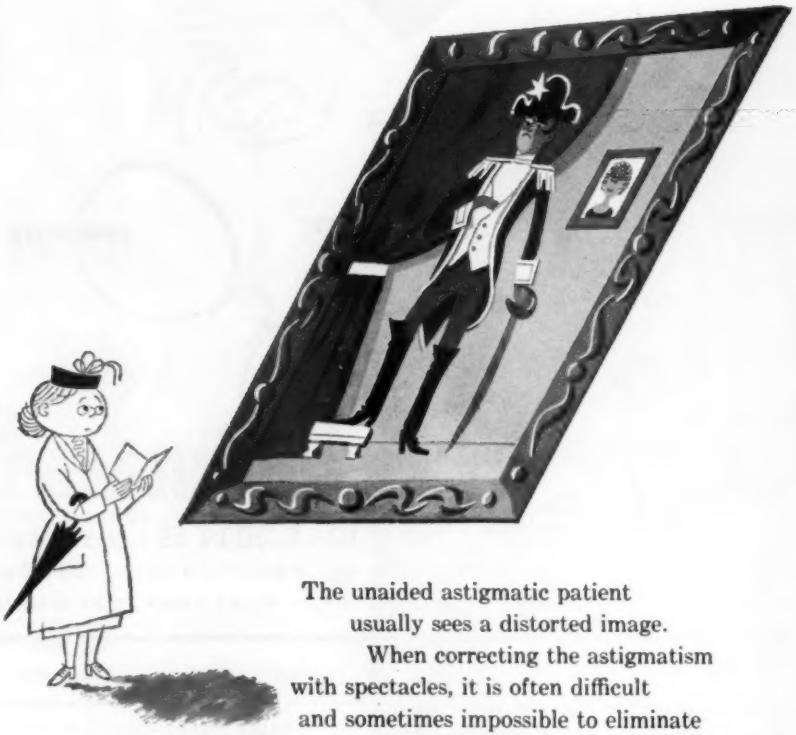

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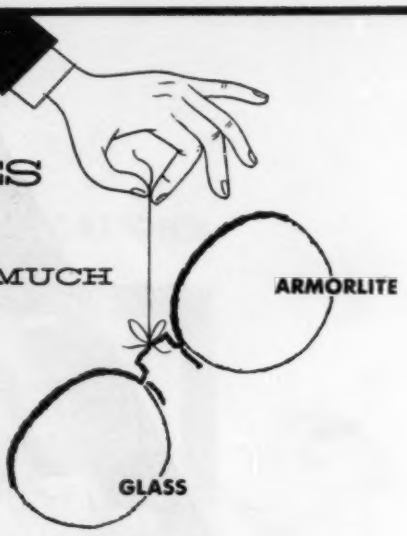

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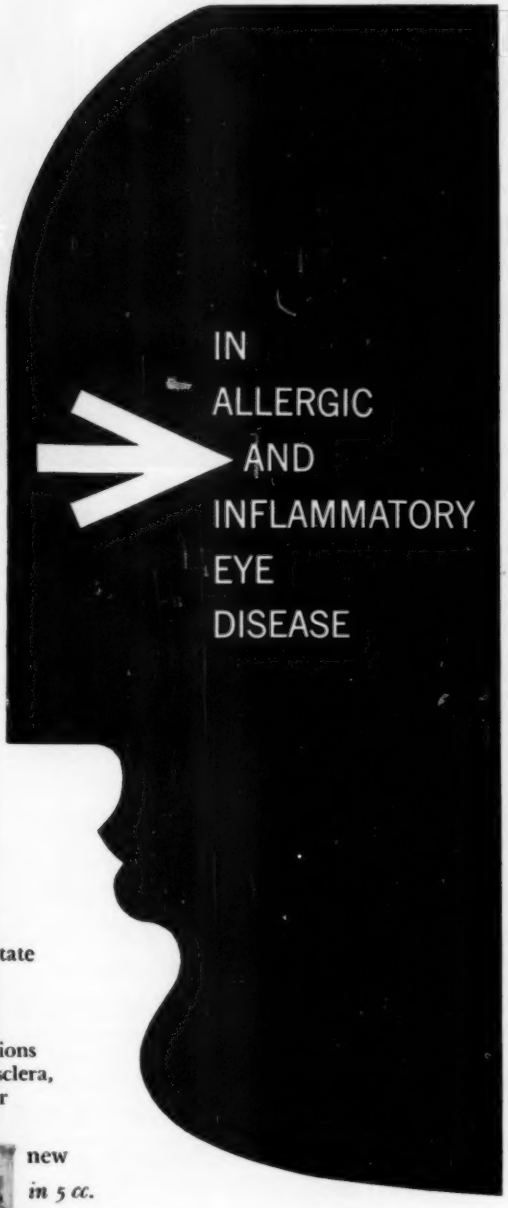

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Corneal Epithelial Changes Occurring During Chloroquine (Aralen) Therapy

LARRY L. CALKINS, M.D., Kansas City, Kan.

The occurrence of visual complaints coincident with the therapeutic use of chloroquine for a variety of clinical entities has been repeatedly reported since 1948.

The ocular side effects have been described in several ways. Alving et al.,[1] in studies of the long-term use of the drug in two groups of 20 volunteers, found that higher dosages produced visual disturbances, headache, bleaching of hair, electrocardiographic changes, and weight loss. No detailed examination of the patients with visual disturbances was reported. Within the first week of therapy Conan et al.[5] described disturbances of accommodation in patients receiving the drug for amebic abscess. The ocular complaints are not evaluated further in this article. Findlay[8] cites Berliner et al., showing that 18 of 32 volunteers had eye symptoms when 400 mg. of chloroquine was used daily. The complaints varied from "blurring of vision" and "a heavy feeling about the eyes" to "something being wrong with the eyes." No detailed biomicroscopic or other examination of the eyes was reported. It was recommended that further evaluation of the drug be carried out before it was given to persons driving a car or piloting an airplane. Rehfuss et al.[19] refer to a disturbance in accommodation in a paragraph on toxicity of chloroquine diphosphate, but there is no elaboration. Shookhoff,[24] in a report on the use of chloroquine diphosphate (Aralen) for amebic dysentery, describes only "interference with visual accommodation." Patel[15] reports changes in accommodation in a small series of patients receiving this drug for amebic abscess of the liver. Weiser et al.,[26] in analyzing 50 patients given chloroquine for amebiasis, found that most patients complained of blurring of vision. Wilkinson[27] gave chloroquine to 52 patients with hepatic amebiasis and, in conjunction with other side-effects, mentioned "blurred vision" without elaboration. Conan,[4] in the treatment of hepatic amebiasis with chloroquine, described the side-effect of disturbed ocular accommodation in one patient. Of particular interest was the reference to lenticular opacities in a single patient by Calnan in a personal communication to Scott.[23] The age of the patient, the biomicroscopic findings before and after therapy, and other specific ocular changes were not cited.

The specific references noted and many others referring to the side-effects of the use of this drug fail to establish the true nature of any specific ocular changes to account for any of the varied ocular side-effects.[3,5-7,9-11,13,14,16,20-22,25]

Submitted for publication July 7, 1958.

Report of Cases

Seven clinical cases receiving chloroquine therapy for a variety of diagnostic entities are presented in which adequate cause for several different ocular complaints is described.

CASE 1.—A 64-year-old white salesman suffered from partially disabling rheumatoid arthritis for many years. In 1955, when his condition was becoming worse in spite of all medication used up to that time and he was having difficulty in maintaining a steady pace in his job, he was started on 250 mg. of chloroquine diphosphate (Aralen) four times a day. After a period of several weeks he was better, and, even with a slightly smaller dosage, he continued to improve with time. About February, 1956, for reasons unknown to the patient except that he had had some mild skin eruptions and paresthesias, chloroquine was discontinued and he was given prednisolone therapy. During the next 18 months, he began to have considerable joint discomfort again, and finally he began to loose time from work. He requested that chloroquine therapy be resumed, and he was given 250 mg. four times a day, in addition to a maintenance dose of prednisolone. Later this was reduced to 250 mg. twice daily. Between four and six weeks after resuming chloroquine therapy, he began to notice some blurring of vision and halos around lights at night, first in one eye and soon in both eyes. His complaints about his arthritis soon disappeared for the most part, but his visual complaints persisted and became severer. He consulted his local ophthalmologist, and several types of local medication were tried, with a working diagnosis of bilateral disciform keratopathy. No improvement resulted.

On Feb. 14, 1958, he was referred to me. At this time the visual acuity was 20/20 and J-1 in each eye with the worn correction. The entire anatomical examination of the eyes was normal except in relation to the corneas. The entire central three-fourths to five-sixths of each cornea showed diffuse epithelial opacification of an irregular fine, almost dust-like character, with whorl intensification at irregular intervals beginning near the apex and extending in spoke-like fashion toward the periphery. This did not appear to involve the underlying Bowman membrane. No definite changes could be established in the anterior stroma. The cornea did not stain. The surrounding limbal zone was clear of this change. The eyes were white and quiet. The ocular pressure was 20 mm. of mercury (Schiøtz) in each eye.

Because of uncertainty as to the exact nature of the corneal change and because of the resemblance to the rare vercillate dystrophy (Fleischer), the patient was presented to the staff clinical conference at the University of Kansas Medical Center. It was generally agreed that the corneas were dystrophic and resembled most the type noted. No treatment was recommended.

Comment.—On personal reflection, this diagnosis seemed untenable for several reasons. Historically it had been acute in onset in a man in his middle 60's. A second examination of the patient approximately six weeks later showed the process to be noticeably worse, and the subjective complaints were more marked. Vercillate dystrophy is admittedly a rare disorder.

The coincidence of the use of chloroquine therapy shortly before the symptoms appeared prompted an inquiry of Ralph Jones Jr., M.D., of Miami, Fla., who had had considerable experience with this drug in human volunteers infected with malaria.[1] He had no knowledge of corneal changes from the use of chloroquine, and he referred the inquiry to the medical Director of Winthrop Laboratories, manufacturers of Aralen. An annotated bibliography relating to the side-effects of the use of the drug was supplied by the manufacturer and was immediately very helpful. Since then, additional references have also been searched for some mention of this interesting, but apparently not alarming, complication, or side-effect, of the use of chloroquine.

Approximately 100 ophthalmologists were then polled for similar experiences. In April, 1958, Dr. Frank Newell, of Chicago, Ill., supplied a well-documented case (Case 2), and Dr. George Gsell, of Wichita, Kan., immediately recalled two cases (Cases 3 and 4). Subsequently, several additional cases

have occurred in the practices of other ophthalmologists. Through the courtesy of Drs. Newell and Gsell; Dr. W. J. Marshall, of Springfield, Mo., and Dr. M. Berry and Dr. Earl Padfield, of Kansas City, Mo., enough material has been accumulated to suggest that it would be valuable to solicit the experiences of others in this matter.

CASE 2.—A married female office clerk was examined by an ophthalmologist (F. N.) in 1953. At that time her visual acuity was corrected to 20/20 and J-1 in each eye, and the eyes were anatomically and functionally normal. This examination included a slit-lamp evaluation of the cornea. At the age of 52, she was examined in the dermatological outpatient department of the Billings Hospital in Chicago on Jan. 2, 1957, with the complaint of a "spot on the forehead." Six years previously a small asymptomatic papule first appeared on the upper nasal bridge. A biopsy was performed, and examination of the specimen resulted in a diagnosis of benign lymphocytoma. Remission followed six weekly x-ray treatments.

A biopsy diagnosis of lymphocytoma cutis resulted from a recurrence in March, 1954. Peripheral blood studies were normal. Remission followed a total of 650 r of x-ray. At the time of the visit to the dermatology clinic, on Jan. 2, 1957, a group of papules had been present over the glabella for approximately one and one-half months. Again, except for the dermatological complaint, a review of systems was negative. All laboratory studies were again normal. Biopsy specimens showed essentially the same histologic picture previously described.

The patient was started on chloroquine 250 mg. p. o. b. i. d. on Jan. 10, 1957. Sometime in March she began to complain of a "haze" in front of each eye. She was examined on May 15, 1957, by the same ophthalmologist who had examined her in 1953. The central vision was still 20/20 in each eye. The eyes were still anatomically and functionally normal except that the corneas showed a diffuse involvement of their entire surface with a central area of greater condensation. Initially this appeared as though the epithelium were edematous, but there was no staining. The tension was 17 mm. of mercury in each eye. A week later there appeared to be less corneal edema, and the area now appeared more opaque and was beginning to develop a "whorl" pattern. The patient now complained of halos around lights in addition to generalized "fuzziness." Chloroquine was discontinued at this time. On Aug. 23, 1957, the whorl pattern of change was still present. On Dec. 13, 1957, the corneal changes had entirely disappeared and the patient's subjective complaints were no longer present.

CASE 3.—A 47-year-old white woman was examined by a dermatologist for an eruption of the face, neck, and arms on Jan. 13, 1949. A diagnosis of disseminated lupus erythematosus was made and confirmed by biopsy. On therapy with bismuth subsalicylate, calcium pantothenate, and cortisone at varying periods until 1953, she experienced numerous remissions and exacerbations. In May, 1953, she was started on quinacrine therapy, 0.1 gm. daily; this dose was gradually decreased. In 1954 she had a short course of corticotropin (ACTHAR-Gel). On June 20, 1955, she was started on chloroquine (Aralen), 150 mg. daily. On June 28 she reported to her ophthalmologist (G. G.), complaining of some difficulty with close vision. Slight irritation of the tarsal conjunctiva was present on both lids in both eyes. The visual acuity was 20/15 and J-1 in each eye with the worn prescription. The ocular pressure was 21 mm. of mercury (Schiøtz) in the right eye and 23 mm. in the left eye. Sodium sulfacetamide (Isoptocetamide) 15% solution was prescribed, t. i. d. A previous examination on Nov. 19, 1952, showed the eyes to be anatomically and functionally normal as well, and a note was made that the biomicroscopic examination showed a perfectly clear cornea.

On July 5, 1955, she was given chloroquine, 300 mg. daily, and she continued to take this dosage for four weeks, reverting

to 150 mg. daily thereafter. She again consulted her ophthalmologist on Sept. 10, 1955, complaining of a "film over the left eye and halos around lights." Corrected vision was still 20/15 and J-1 in each eye, but the letters appeared hazy in the left eye. Stereocampimeter and peripheral fields were normal in each eye. Fundus examination similarly was unchanged from previous examination. In the slit-lamp examination, a diffuse haze of the left corneal epithelium was noted that appeared to be made up of minute dot-like opacities which were not very opaque except where they were focally slightly aggregated. Oleovitamin A and sesame oil drops were prescribed twice daily. On Sept. 23 she complained of the same haze over the right eye. Again the vision was not disturbed particularly, but the same slit-lamp appearance described in the left eye was now present in the right.

On Oct. 7, 1955, the haze was noticeably more marked in each cornea and the opacities began to show a whorl-like arrangement due to focal increase in intensity. On Oct. 31 the chloroquine was discontinued. On Nov. 21 the symptoms were still present, but the corneas looked considerably better in the slit lamp. Marked improvement was present in slit-lamp examination on Dec. 14: Symptoms were still present but less bothersome. On Jan. 1, 1956, the corneas were clear and all symptoms were gone. The patient has been examined periodically since that time, and the haze has not returned.

CASE 4.—A 58-year-old white man had had rheumatoid arthritis and hypochromic anemia for several years. He received chloroquine, 250 mg., twice daily and sodium salicylate, 650 mg. three times daily, for an indeterminate period, approximately two to three months. He first complained of visual disturbance and rings around lights to his ophthalmologist (G. G.) on March 1, 1958. He had particular difficulty under artificial lights and while driving at night. He had already worn a cap with a long bill for some time to try to cut down the glare and reflection from lights.

His vision with a moderate hyperopic correction was 20/20 and Wells No. 1 in each eye. Slit-lamp examination showed a fine droplet-like change in the epithelium of the cornea which was seen best as a fine cloud with indirect illumination. The corneal stroma appeared normal. This resembled, almost as a mirror image, the changes seen in Case 3.

Chloroquine was discontinued on April 1. There was no subjective improvement until May 9. The light still bothered him somewhat at this time. On May 29 the corneas were clear and all symptoms had disappeared.

All other features of the external, anterior segment, and internal examination of the eyes were normal at all visits.

CASE 5.—A 52-year-old white woman was first examined in February, 1958, at which time she gave the history of a blood vessel rupture in the right eye 28 years previously. This had been followed by a cataract in the left eye. She had only recently received new spectacles and was having periodic discomfort in each eye; both eyes had been red for several days.

Examination showed the visual acuity to be finger counting at 2 ft. on the right and 20/40 left. There was a bilateral serous iritis. The right pupil dilated well, but the left was bound down by ring synechia. Under local therapy, consisting of corticosteroids and atropine, the right eye responded well, but the left showed only focal dilatation of the pupil, and a one plus flare and cells remained. Subsequently systemic steroids and a pyrogen (Piromen) were used, but they did not cause the left eye to clear entirely. In the meantime local therapy to the right eye was discontinued. Except for punctate K. P., which were thought to be consistent with the nature of the inflammatory disease and were seen only initially, the corneas were clear at all times in the biomicroscopic examination.

On March 10, 1958, the patient was placed on chloroquine diphosphate, 250 mg. four times daily. On April 17 she complained of feeling "nauseated and weak in

the knees." The dosage of chloroquine was reduced to 500 mg. daily. On April 28 both corneas showed diffuse haziness, which was also patchy in character. The left eye was still under treatment with a corticosteroid (Isoptohydrocortisone) every two hours and atropine 1% solution three times daily. The chloroquine was discontinued on this date. On May 9 the corneas showed no change in the slit-lamp appearance. On May 23 there was again no change in the corneas, but the patient was much improved with regard to her iritis, and reduced amounts of atropine and local corticosteroid were recommended. The visual acuity in the left eye was improved to 20/30+ at this time. On June 10 only minimal epithelial haze remained and the patient was subjectively improved as reported by her ophthalmologist (E. P.).

CASE 6.—A 47-year-old white woman had been under therapy with a variety of therapeutic agents for approximately 20 years for lupus erythematosus. Chloroquine was started, 250 mg. three times daily, on Feb. 12, 1958. Ten days later the dose was reduced to 250 mg. daily. She complained by mid-March of some blurring of vision described as a "fuzziness around objects which she seemed otherwise to see just as well in other respects," and "halos around lights at night." She first consulted an ophthalmologist at this time and was treated for glaucoma with pilocarpine 3% preparation four times a day. This ophthalmologist had observed the patient over a period of four years and had recorded borderline tensions on numerous occasions, but he had noted no field cuts or disturbance in the central visual acuity.

On May 6, 1958, when the halos seemed to be more intense and the fuzziness of her vision was not improved, she visited a second ophthalmologist (E. P.). There had been no administration of pilocarpine for over 14 hours at the time of the visit. The central visual acuity was 20/25 and Wells No. 1 in each eye with correction. The pupils were 5 mm. in diameter and reacted well to all stimuli. The anterior chamber was deep. The ocular pressure was 22 mm. of mercury (Schiøtz) (55 scale) in each eye. The remainder of the anatomical and functional examination was normal except for the examination of the corneas, which showed diffuse epithelial haze, resembling but not characteristic of bedewing, with focal curvilinear increases in density. The area of Bowman's membrane and anterior stroma appeared not to be involved. Chloroquine was discontinued.

By May 20 her systemic symptoms had reappeared and her bones ached. Halos were still present but less marked. The visual acuity was 20/20 right and 20/25 left. She had not received pilocarpine since her first office visit, and the ocular pressure was 23 mm. in the right eye and 20 mm. in the left eye. Objectively the biomicroscopic examination of the cornea showed definite clearing but some residual central change.

CASE 7.—A 50-year-old white woman was given 250 mg. of chloroquine once daily beginning Dec. 10, 1957 for primary scleroderma. There was noticeable clinical subjective improvement in approximately three to four weeks. She was first seen by an ophthalmologist on May 15, 1958, at which time she complained of some blurring of vision manifested by a halo of fuzziness about objects, particularly about lights, which had been present for several weeks. The visual acuity was 20/20 and Wells No. 1 in each eye with correction. The tension was within normal limits. All of the anatomical and functional examination of the eyes was normal, except for the examination of the cornea in the slit lamp. There was a diffuse epithelial and questionable subepithelial haze with focal curved spoke-like increases in density seen best with retroillumination and sparing perhaps the peripheral 0.5 to 1 mm. of cornea at the limbus. Chloroquine was discontinued. On June 10 the ocular complaints were less marked and some, though not marked, improvement in corneal changes was reported.

Analysis of Cases

History.—Some type of visual impairment was present in all cases. This varied from the complaint of "a film over the eye," and "a haze over the eyes," to a "glare in the sunlight" making sunglasses mandatory and "halos and rings around lights." No patient complained of local ocular irritation, pain, redness, or discharge except the patient for whom the drug was used in treatment of iritis.

The drug was administered in varying dosage, with those who received a slightly higher dosage developing symptoms and signs earlier. Those receiving 250 mg. three to four times a day developed halos and had demonstrable corneal epithelial deposits in four to six weeks, while those given a smaller dose had symptoms and signs after a longer interval.

At least one patient had been treated for glaucoma which has not subsequently been established by provocative test or visual disability. One patient was referred to an ophthalmologist because the referring physician thought glaucoma should be ruled out.

Nearly all patients who drove automobiles felt insecure about the management of the car in night driving because of the halos and general fuzziness of the lights of approaching vehicles.

Symptoms and objective corneal changes were not favorably affected by any local medication.

Ocular Examination.—In spite of the severity of the complaint regarding the blurring of vision, the actual visual acuity was not materially affected when measured on the Snellen test chart indoors. Out of doors or in a very brightly lighted room there was a noticeable reduction in the visual acuity in one patient tested in this manner. None of the patients under testing circumstances showed any appreciable specific effect on the accommodative mechanism except for the single case of anterior uveitis, where atropine was also used. Except for this same case all changes were limited to the cornea and consisted of diffuse fine droplet-like change and opacity limited to the epithelium and possibly some subepithelial areas, but not involving Bowman's membrane. Some cases of longer standing showed focal linear increase in this opacity, resembling the spokes of a wheel slightly curved. Earlier the change in the epithelium resembled edema, and it required examination with the slit lamp in order to identify and to locate the change. Retroillumination was found to be the best method for early identification. Advanced changes (Case 1) can be seen with the naked eye and the pocket flashlight. The epithelial surface remains smooth early, and in no case, regardless of the degree, was there a break in the epithelium which would stain with fluorescein. The visual fields were full and without abnormal scotomata in all cases tested. The ocular pressure was not elevated above the normal scale in a single patient.

Therapy.—Chloroquine was discontinued in all cases except one (Case 1). In all patients except Case 1, the subjective symptoms and objective corneal changes have either markedly improved or completely cleared at this writing. In Case 1, where chloroquine has been continued, the corneal changes have been progressive, though very slowly. Symptoms are more marked and some actual visual loss is now measurable even in subdued light.

Comment

Corneal changes are produced in certain persons receiving chloroquine therapy which are similar to those reported in patients receiving quinacrine (Atabrine) reported by Chamberlain and Boles [2] and by Reese [18] in 1946. Similar objective changes and clinical complaints were recorded in persons involved in the manufacture of Atabrine in England by Mann.[12] These persons did not take the drug but were only exposed to the dust in its manufacture. Mann reproduced essentially the same changes in animal eyes by insufflation under controlled circumstances. From this work it was suggested

that the material in the epithelial area was 2-chloro-7-methoxypicridone, which is an exceedingly insoluble substance only slowly formed by hydrolysis of Atabrine. These changes were reversible on removal of the subjects from the exposure and would reappear on reexposure. Chamberlain and Boles [2] and Reese [18] showed that an appreciable number of the patients showing this change also had or developed hepatic dysfunction. This has not been the experience with chloroquine, which has one of its major uses in the treatment of hepatic amebiasis.

Because of the obvious widespread clinical value of chloroquine in a variety of disease entities, there is no desire to cause undue alarm in its use in accepted dosage. Rather, it is the intent of the publication of these findings, which have been carefully checked, to encourage the specific search for the corneal change in patients receiving the drug and the identification of the substance in the cornea, in order that methods of controlling the corneal change might be developed while the patient continues the use of this important therapeutic agent.

The nature of the clinical entity for which the drug was administered is apparently not a contributing factor, since several diagnoses are represented in the seven cases reviewed. Currently studies are under way to determine, if possible, the nature of the corneal deposits or epithelial change. Correlated series of patients from the same clinic receiving chloroquine and other medications are to be evaluated biomicroscopically and with regard to other ocular functions. Hepatic function studies will be obtained from patients before and after the institution of therapy.

Summary

Seven cases of bilateral corneal epithelial change associated with the therapeutic use of chloroquine (Aralen) are presented in detail.

Visual impairment was the presenting complaint; it was always bilateral. Though the central visual acuity was not materially affected when tested indoors, the principal complaint had to do with a fuzziness about objects observed in bright light and a dispersal of lights at night (halos).

Variable doses of chloroquine were in use for a variety of clinical entities. Those receiving larger doses developed symptoms earlier than those on relatively smaller doses. In some, but not all, cases, chloroquine was the only drug in use.

Examination showed diffuse haziness of the epithelial and possibly subepithelial area of each cornea of every patient. In some, where the change was more advanced, there were local increases in density, forming curvilinear spokes with the apex at the center and resembling a rare dystrophic change, vercillate dystrophy (Fleischer). The stroma was not involved in the cases described. There was no other evidence of ocular disease, except in a patient receiving the drug for the treatment of iritis. The biomicroscope is necessary for early identification of corneal changes; advanced cases can be seen macroscopically.

All patients have either markedly improved or have become completely free of symptoms upon discontinuing the chloroquine. One patient, who has continued to take the drug, has shown an increase in subjective complaints and a definite increase in objective corneal change.

The corneal change described here is similar to changes previously described in the corneas of patients receiving quinacrine (Atabrine).

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George Frick

Factors Influencing Early Nineteenth Century Ophthalmology

PAUL TOWER, M.D., Los Angeles

To the practitioners of Baltimore early in the last century, George Frick was a respected colleague who applied to the specialty of ophthalmology great effort and profound thought. To medical historians his eminence in ophthalmology is contingent upon his "Treatise on the Diseases of the Eye," the first American textbook on the subject. Accordingly, the position of "Father of American Ophthalmology" has been assigned to him and the profession has generally accepted him as such.

Those early days of the dawn of specialization saw the commencement of an international rivalry leading to factional disputes among American ophthalmologists. Controversial opinions arose between English-oriented and German-oriented oculists, with Hays and others representative of the British school in Philadelphia and New York and Frick representative of the Viennese school in Baltimore, thus suggesting that an analysis of the differences between the British and Viennese attitude was reflected in the response of his contempories to George Frick. Neither school had utilized the advances then current in physics and ocular physiology.* For instance, in the person of Thomas Young, England made an extraordinary contribution to physiologic optics, but in his lifetime ophthalmology took no perceptible notice of this or other contributions in the basic sciences. The study of eye diseases had not progressed to the point where it could have been placed on a truly scientific basis. This happened only in the second half of the nineteenth century, and if this development is to be linked with one name that name is, of course, Hermann von Helmholtz.

Frick was criticized for following the German school with its minute distinctions and precise definitions, but this criticism of German exactness was not unusual at the time. In the 1821 French edition of Scarpa's [2] book on ophthalmology, similar sentiments appear,† and in 1824, Travers [3] confesses that he can not read German but that Englishmen who can, tell him that Beer's work is comprehensive and exact. Then there follows these remarks. "I should be sorry to see the sober sense of my countrymen perverted by a taste for fastidious distinctions. Simplicity is the characteristic feature of English surgery, which is neither more nor less than the application of the principles of inflammation, as illustrated by the genius of John Hunter."

"Scientific study trips" [4] became increasingly popular with five out of six ophthalmologists in search of scientific advances traveling to England (London and/or Edinburgh). Only two out of six went to Vienna, and only one to Berlin. In other words, Britain was the point of reference, scientifically speaking, but the situation changed in the second half of the century, with Vienna and Berlin becoming the chief fountainheads of ophthalmology. Frick's stay in Vienna in 1817 coincided with the completion of Beer's impressive two-volume work, whose doctrines dominated ophthalmology for many years. As director of the University eye clinic Joseph Beer had already maintained a European reputation for a decade as a surgeon and teacher,[5] and among his students were such prominent eye

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* Hirschberg,[1] pp. 381-465.

† Hirschberg,[1] pp. 342-343.

doctors of the period as Carl Ferdinand von Graefe (father of the well-known Albrecht von Graefe), Langenbeck, Jaeger, and others. Consequently, once Frick came under the influence of Beer, he followed him to the exclusion of domestic and British contributors, thus indorsing German scientific advancements. Not many years later the average ophthalmic-minded practitioner in the United States began to reveal his predilection for German ophthalmology and to follow the road to Vienna for postgraduate work.

Our country was beginning to show increasing stability after the War of 1812; Europe was at peace again after the Battle of Waterloo, and ocean travel was safer. Napoleon had been deposed, and peace between the United States and Britain had been established. Finally, the first International Congress of Ophthalmology met at Brussels in 1857. Here in a paper Gross ‡ expounded a rather critical appraisal of Frick, subsequently endorsed by Hirschberg.[4] It was made obvious that Frick and his contemporaries had been good surgeons and commendable teachers and writers but that the fact remained that they had made no original contributions of lasting value to ophthalmic science. In other words, the time of American ophthalmology had not arrived.

Apparently Frick had put his whole soul into the support of German ophthalmic advances, and he appeared ready to defend them. In the *Philadelphia Journal of the Medical and Physical Sciences* in 1827, there appeared a review of a work by A. D. Krohn on the operation for artificial pupil.[6] The review of this essay is in itself of no special interest, but, after quoting extensively from Krohn's thesis, the reviewer adds the following paragraph. "For an account of the operations, we must refer the reader to Dr. Frick's work on the eye, heretofore analyzed in this journal, which every American practitioner ought to possess, who is desirous of becoming acquainted with German Ophthalmology." Hirsch [7] substantiates this with the observation that in North America George Frick appeared on the scene expounding the teachings of the Viennese ophthalmic school. This statement finds its repetition in the assertion of Baas [8] that German ophthalmology found its representatives in Liebreich in London and Frick in Baltimore.

‡ Samuel D. Gross was one of the founders and chief editors of the *North American Medico-Chirurgical Review*. In 1857, he was the American delegate to the First International Congress in Brussels.

Biography

The three American pioneers of distinction in ophthalmology during the early nineteenth century were Frick, Hays, and Littell. Although they were all outstanding in their chosen specialty, taking up the gauntlet for progress and improvement in ophthalmic practice, it is the name of George Frick (Fig. 1) that has attained the greatest prominence. He was born in Baltimore in 1793.§ After an excellent education in the liberal arts and sciences, he entered the Medical Department of the University of Pennsylvania and received his degree in 1815. In 1817 he was admitted to practice by becoming a licentiate of the Medical and Chirurgical Faculty of Maryland.[9] His enthusiasm for the science of ophthalmology reached its maximum in Vienna, after he became acquainted with the great Beer, whose diagnostic interpretations and clinical instructions evidently made a deep and lasting impression on him.‖ Progressive deafness gradually restricted his activities until finally he was forced to terminate his successful Baltimore practice in 1840 and to retire to Dresden, Germany, where on March 26, 1870, he died.

§ This is contrary to the observation that Frick was German-born, made by August Hirsch in "Biographisches Lexikon der hervorragenden Ärzte aller Zeiten und Völker," Vienna & Leipzig, Urban & Schwartzenberg, 1884, Vol. 1.

‖ Apparently Frick was an auditor and observer at Beer's clinic, since a search does not reveal his name on the official register (personal communication to the author from F. Gall, Archives of the University of Vienna).

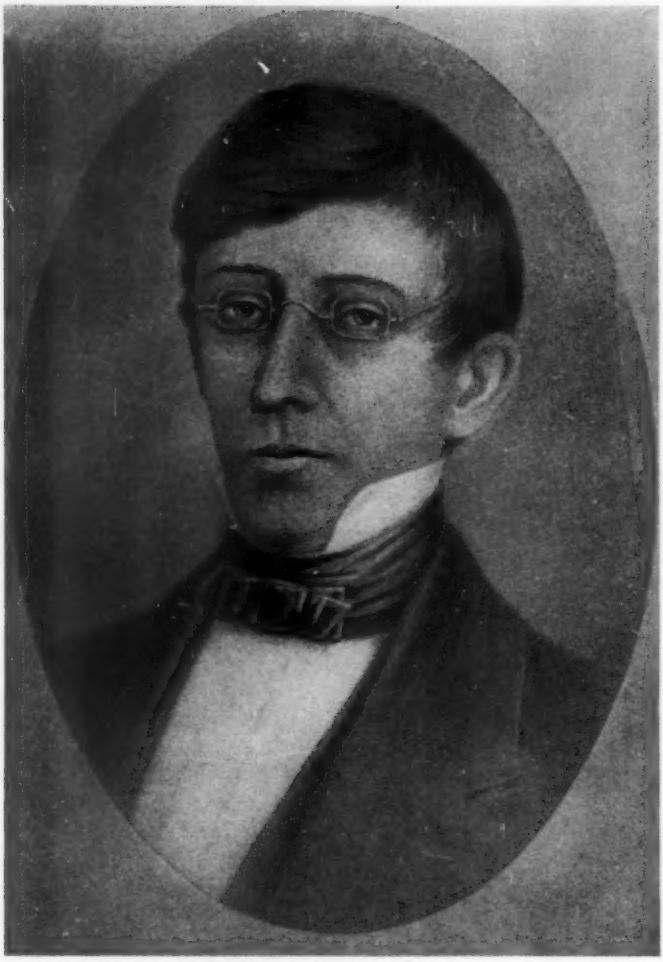


Fig. 1.—George Frick.

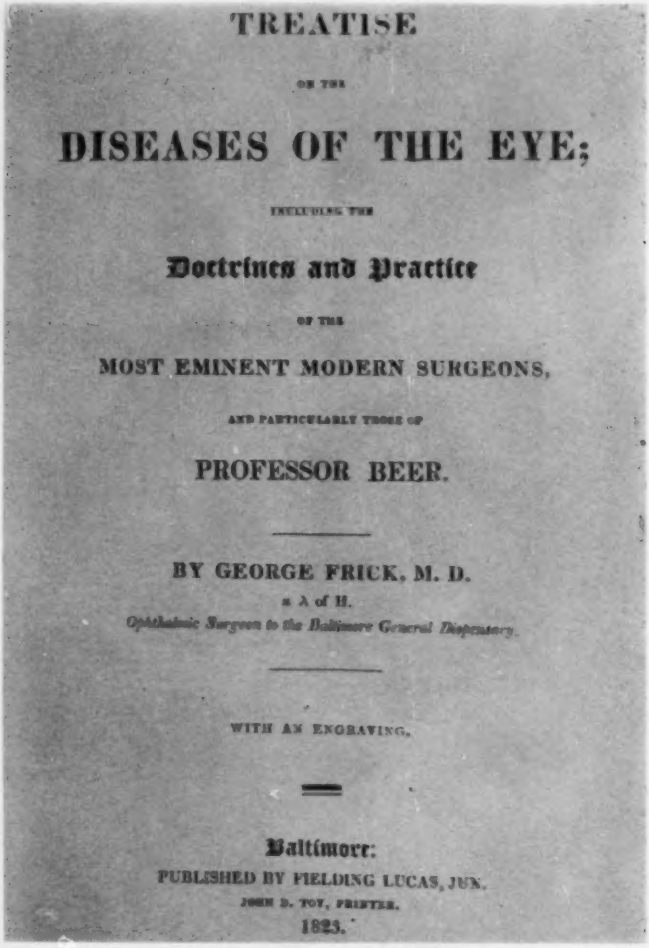
The articles which he has contributed to the literature of the profession are the following: "On the Meloe Vesicatorium," his thesis for the degree in medicine in 1815; papers on observations on "Cataract and the Various Modes of Operating for Its Cure," in the *American Medical Recorder* in 1820-1821; "Observations of the Various Forms of Conjunctivitis" (*American Medical Recorder,* 1821), and "Observations on Artificial Pupil and the Modes of Operating for Its Cure" ¶ (*American Medical Recorder,* 1823).

¶ The mistake in the title is obvious.

The only book he ever wrote was "A Treatise on the Diseases of the Eye; Including the Doctrines and Practice of the Most Eminent Modern Surgeons and Particularly Those of Professor Beer," published in Baltimore in 1823 (Fig. 2).#

Frick's participation in the activities of his community is conspicuously noteworthy. In 1821, he was elected secretary of the District Medical Society representing the Medical and Chirurgical Faculty residing in

A second edition with no change, except for numerous notes by the English surgeon Richard Wellbank, appeared in London in 1826.


TREATISE

ON THE

DISEASES OF THE EYE;

INCLUDING THE

Doctrines and Practice

OF THE

MOST EMINENT MODERN SURGEONS,

AND PARTICULARLY THOSE OF

PROFESSOR BEER.

BY GEORGE FRICK, M. D.

M. M. S. of H.

Ophthalmic Surgeon to the Baltimore General Dispensary.

WITH AN ENGRAVING.

Baltimore:

PUBLISHED BY FIELDING LUCAS, JUN.

JOHN D. TOY, PRINTER.

1823.

Fig. 2.—Title page of Frick's book.

Baltimore. In the year 1822, the laws and by-laws governing the faculty, together with a list of officers and members, was published by its order, listing Frick as one of the examiners.[10] In 1819 George Frick met with Drs. Ducatel, Williamson, and Macaulay in Baltimore (in a room over a stable) and they organized the Maryland Academy of Sciences. From 1821 to 1823 he was vaccine physician, which office the city had created one year previously upon recommendation of the Medical and Chirurgical Faculty. The year 1822 found Frick lecturing on clinical medicine in the Maryland Hospital. From 1821 to 1826 he occupied the office of secretary of the Medical and Chirurgical Faculty. In 1823, he was ophthalmic surgeon at the Baltimore General Dispensary, and in 1830 he occupied the unique position of Professor of Natural History at the University of Maryland.[10]

Frick's Textbook

For several years Frick's manual was among the books required to be read by the graduating students before they could become eligible for examination.[10] The book was received with enthusiasm. Of the two

American reviews that appeared, the one in the *Philadelphia Journal of Medical and Physical Sciences* (probably written by Isaac Hays),[11] although critical of certain parts of the book that conflicted with British viewpoints, was nevertheless summarized as follows. "The author evidently possesses a cultivated and well disciplined mind. To those who are entering upon the study [ophthalmology], the work of Frick will be a most useful manual; it is moreover the first American work that has appeared on the subject, and as such is worthy of every encouragement." The other review in the *Medical Record*[12] presented the following concluding commendatory reflection. "Offering the humble tribute of our thanks to the author for the benefits which he has conferred on the profession generally, by presenting them with a volume of great value and utility, and one which was much wanted. As a manual of the diseases of the eye, we believe it to be the best which has been published. It contains all the improvements which have enriched ophthalmic surgery, in such a surprising degree, within a few years past; and the author has spared no pains to make his work a valuable treasure, for study as well as reference, thereby rendering it equally useful both for the practitioner and the student." The German commentaries, on the other hand, were noncommital but expressed surprise that Frick had omitted entirely American ophthalmologists, including only Europeans and among these only Germans, as for example Beer, Langenbeck, Himly, and others.[13-15]

Remaining alone in its field for a number of years, the book was an appropriate beginning for American ophthalmology, comprising a classification and account of all the presumably known ocular diseases. The whole was arranged in four parts: "I. Ophthalmia"; "II. Of the Diseases Which Attack the Individual Textures of the Eye"; "III. Of the Diseases of the Appendages," and "IV. Of the Diseases Which Attack the Eyeball."

Ophthalmitis, or "pure inflammation of the eye," is the first subject treated under the general head of ophthalmia, for which no definite cause could be found, because its etiological development was veiled in darkness. The use of leeches is recommended, applied to the inner canthus or immediately over the facial vein. Also advocated are scarifications of the globe, "provided they are numerous, deep, and bleed freely," as well as the excision of small portions of the inflamed conjunctiva immediately around the cornea. Astringent collyria are condemned, but tepid fomentations are advised and cold astringent washes are recommended after the acute inflammation has subsided. Gonorrheal ophthalmia was to Frick a disease of very doubtful existence. He had never seen a case. The cases communicated to the medical world by Swediaur, Beer, Scarpa, and Vetch induced him to give it a place in his work with the observation that such a form of conjunctival inflammation may exist. Catarrhal, strumous, and purulent inflammations are described, and the distinctions between them are enumerated in a precise manner. Most practitioners had been treating the members of this group in much the same manner, without considering the various minutiae as presented by Frick. Under purulent ophthalmia, the susceptibility of young children to the affliction is pointed out and the "affinity it bears to Egyptian ophthalmia" is discussed. An entire chapter is spent on so-called rheumatic ophthalmia, and its involvement of the sclera is stressed as the "original and principal seat of the disease."

Iritis is described and divided into idiopathic, syphilitic, and gouty. The possibility is presented of its occurrence from various external causes as well as in some peculiar diathesis of the whole system. Heat and strong infusions of poppy water are recommended. It is established that to prevent contractions of the iris and its subsequent adhesion to the lens capsule a weak solution of belladonna or hyoscyamus should be used twice daily.

"Amaurosis, gutta serena, or suffusio nigra" are some of the terms applied to that species of blindness produced by some im-

mediate disease of the optic nerve or retina or combined with some other affection of the eye or general system. Of course, the golden age of the ophthalmoscope had not yet arrived, and "the thousand natural shocks that flesh is heir to" in intraocular disorders had not as yet been ascertained. The treatment of these concealed conditions was divided into general and local—purging and the topical use of irritants.

In discussing cataracts, the necessity of ascertaining whether the cataract is complicated with any affection of the general system or derangement with other parts of the eye is particularly stressed. Described are the methods of extractions, couching, or depression and "breaking up the lens" (discission). The ever-present question of the propriety of performing the operation for cataract when only one eye is involved was then also a bone of contention, and Frick contented himself with merely stating the usual arguments on both sides, without throwing his opinion into either scale.

Comment

George Frick lived to see the decline of the English influence and the gradual predominance of the formulated scientific research of the Germans. In fact, ophthalmology was advancing so rapidly that although at the original date of publication Frick's textbook was undoubtedly most authoritative and up-to-date several years later it could fulfill no longer its original aim. Yet he wrote not only with conviction but with delicacy of phrasing and dignified reserve, so that even now his work is readable and enjoyable.

The stimulus imparted by the work and success of some is often the motive which impels individual effort on the part of others. Thus Beer's compelling influence was obvious and gave considerable impetus to Frick's endeavors.

Respected and honored by all who knew him, his virtues had secured for him the affection of his friends, his competence and industry, the respect and esteem of the community in which he lived, and a reputation of no ordinary character in a wider circle. Ophthalmology cherishes his memory as that of one who established his claim to be held in perpetual remembrance.

2007 Wilshire Blvd. (57).

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Contralateral Glare Effect on the Fusion Frequency of Flicker

ERNST SIMONSON, M.D., Minneapolis

The fusion frequency of flicker (FFF) depends upon the condition of all visual pathways, and decrease of the FFF by lesion in various parts of the visual pathways has been demonstrated. Yet, there is strong evidence that in the case of intact ocular structures the FFF is determined in the occipital cortical centers. The evidence includes photodriving, decrease of the FFF in brain pathology, binocular summation effect, and reflex changes, and it was reviewed by Simonson and Brozek.[1] The reflex changes of the FFF are of particular interest for experimental differentiation between peripheral and central components of the visual pathways, because diagnostic tests could readily be developed on this basis. In an earlier study on the effect of caloric vestibular stimulation, a statistically highly significant differentiation between 16 normal subjects and 16 patients with postconcussion syndrome was obtained.[2] The FFF decreased in all normal subjects and increased in 14 patients, while 2 patients showed no change. However, reflex responses involve, in addition to the visual pathways, other receptors, and their functional state may be a determining factor. It seemed to be of interest, therefore, to study an interaction phenomenon involving only the visual pathways.

The binocular summation effect is of interest in this respect because it also involves central interaction. The statistical significance of Sherrington's early observations is questionable, but Ireland[3] found the FFF in binocular in-phase stimulation significantly higher, and in binocular out-of-phase stimulation significantly lower, than in monocular presentation. However, we found the variability of the binocular summation effect so large, in view of the relatively small differences, that we abandoned this approach.

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From the Department of Ophthalmology and Laboratory of Physiological Hygiene, University of Minnesota Medical School.

Method

The FFF was determined on the left eye at a visual field of 1.5 degrees and a 50:50 light-dark ratio with square wave form of the light stimulus, with use of an electronic flicker apparatus.[4] The Sylvania glow modulator tube served as the light source. The subject's chin rested on an adjustable chin-rest. Surrounding illumination was kept constant at 1 ft-c. at the level of the test patch. The right eye was exposed to glare for about one minute, with the left eye shielded by means of a shade. Three readings of the FFF on the left eye were made before and during glare exposure and were averaged. A second observer made sure that full glare exposure was achieved, eliminating the possibility of voluntary or involuntary diminished glare effect through eye movements or blinking.

In preliminary experiments, the effect of artificial pupils was studied at two brightness levels of the test patch, differing by 1:10. Artificial pupils decreased the glare effect at the low brightness level, but not at the high brightness level of 150 foot lamberts. The investigations of the glare effect were made at the higher brightness level

TABLE 1.—*Contralateral Glare Effect on the FFF in Normal Subjects*

Exposure R. Eye, Ft-C.	No.	FFF Mean Before	L. Eye Mean During	Glare Effect Δ Mean	S. D.	*P*
200	30	38.4	37.00	−1.4	2.01	0.007
350	30	37.3	35.3	−2.0	2.06	0.001
500	30	39.3	38.5	−0.8	2.21	0.043

without artificial pupils, for reason of experimental simplicity.

Three groups of 30 healthy older men were investigated, each at one of the three levels of glare exposure. It was not possible to study in the same subjects the three different glare levels, owing to limitation of testing time. The glare effect was studied also in 52 patients with essential hypertension, subdivided into three groups of 17, 21, and 14 men, for glare exposure of 200, 350, and 500 ft-c., respectively. None of the patients showed evidence of cardiac decompensation.

Results

The FFF of the left eye dropped during glare exposure of the right eye at all three levels of glare exposure, as shown for the group means in Table 1. Depression is greatest at 350 ft-c. It is less pronounced not only at 200 ft-c., which might be expected, but also at 500 ft-c. In this respect, the contralateral glare effect located in the visual centers is fundamentally different from direct glare effects, which increase with the brightness of the glare source in all visual functions tested. The drop of the FFF was statistically highly significant at 200 and 350 ft-c.; the smaller drop at 500 ft-c. was significant at the 4% level. The differences in the drop of the FFF at the three glare levels did not reach statistical significance. However, it is interesting that exposure to 500 ft-c. did not produce a greater drop than exposure to 350 ft-c.

The response of the patients with essential hypertension was similar to that of the normal group. The drop was highly significant at 200 and 350 ft-c., and the maximum depression occurred at 350 ft-c. The slight drop at 500 ft-c. did not reach statistical significance, and the mean differences between the groups were not statistically significant. The initial value of the FFF was not lower in the hypertensive patients than in the normal subjects, which contrasts to earlier observations [5,6] but can be explained with the absence of cardiac decompensation in this group.

The standard deviation of the change of the FFF was relatively large in the normal group, indicating considerable individual variability. In fact, in a few subjects the FFF increased, i. e., the contralateral glare effect may occasionally produce excitation, although depression is commoner.

In the groups of hypertensive patients, the standard deviation was smaller than that of the normal groups at 200 and 350 ft-c., indicating greater uniformity of response.

In view of the variability of response, the extreme depression and extreme excitation appeared to be of interest, together with a distribution of major changes exceeding ±2.0 CPS (Tables 2 and 3).

TABLE 2.—*Contralateral Glare Effect on the FFF in Patients with Essential Hypertension*

Exposure R. Eye, Ft-C.	No.	FFF Mean	L. Eye Mean	Glare Effect Δ Mean	S. D.	*P*
200	17	39.6	38.4	−1.3	0.90	0.001
350	21	36.7	35.1	−1.6	1.66	0.003
500	14	39.6	39.0	−0.6	2.17	0.32

TABLE 3.—*Distribution of Extreme Reactions of FFF in Left Eye, on Glare Exposure of Right Eye*

Glare Exposure, Ft-C. Normals	Highest Depression	Highest Excitation	>−2.0		>+2.0		Subjects, No.
			No.	%	No.	%	
200	−7.2	+3.2	13	43	2	6	30
350	−5.3	+3.0	15	50	1	3	30
500	−5.2	+3.8	8	26	3	10	30
Hypertensives							
200	−3.0	+0.5	4	23	0	0	17
350	−4.6	+1.5	11	52	0	0	21
500	−4.6	+3.0	4	28	2	14	14

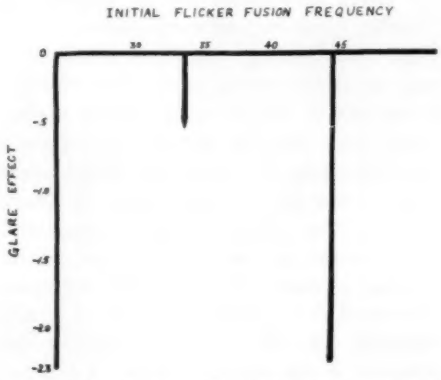
It is recognized that the small size of the samples limits the statistical significance; extension of the extremes should be expected with enlargement of the sample. Even so, the magnitude of the extreme depressions in the normal and hypertensive groups is large, and this is true also for the extreme excitation in the normal group. In a few persons, the contralateral glare effect approaches the largest changes of the FFF obtained in acute experimental conditions.

The statistical significance of the distribution was evaluated by means of the χ^2-test. The greater incidence of larger depressions than that of larger increases was statistically significant at the 5% level for the 350 ft-c. level, both in the normal and in the hypertensive group; it nearly reached statistical significance for the 200 ft-c. level in the normal group, but not in the hypertensive group. Pooling the groups at the 200 and 350 ft-c. levels resulted in high statistical significance (at the 1% level) of the greater incidence of the larger depressions in both groups. On the other hand, the greater incidence of larger depressions was statistically not significant at the 500 ft-c. level in both groups. This is additional evidence for the maximum glare effect at the level of 350 ft-c. in the group averages in Tables 1 and 2. Obviously, the smaller mean decrease of the FFF at the 500 ft-c. level is due to the greater incidence of excitation.

For analysis of a possible relationship between the initial FFF and its change under contralateral glare, 24 of the 90 subjects with the lowest initial values and 24 with the highest initial values were compared, pooling the three glare levels. The results are shown in the Figure. The average initial FFF values in these two groups were 33.6 and 44.4, respectively, and there was no overlap of individual values. The mean change in the FFF in the group with low initial FFF under glare was −0.546, and in the group with high initial FFF it was −2.271. The difference of the glare effect was statistically highly significant ($P<0.01$). Persons with high initial FFF show, on the average, a more marked contralateral glare effect than persons with low initial FFF.

Comment

The most important result is the demonstration of a contralateral glare effect, involving only the visual pathways. Since glare exposure of the right eye, as well as the flicker exposure of the left eye, stimu-



Contralateral glare effect in 24 subjects with the lowest, and 24 subjects with the highest, initial FFF, out of a total group of 90 subjects.

lates both the ipsilateral and the contralateral occipital cortex, the anatomical contralateral glare effect is not necessarily a functional contralateral effect.

The contralateral glare effect has some parallel in ERG investigations, which also have some bearing on the possible localization. Müller-Limroth [7] found in guinea pigs a consensual response of the ERG to light exposure of the contralateral eye, after elimination of the anterior part of the eye, including the iris. The pathway from the illuminated eye crossed through the chiasma to the lateral geniculate body and was conducted from there centrifugally to the retina. In the guinea pig most of the optic fibers cross the chiasma; it is reasonable to assume, therefore, that in man the ipsilateral and contralateral geniculate bodies would be involved. Granit [8] observed potentiation and occasionally inhibition of the spike-frequency in the ERG on stimulation of the reticular substance in the tegmentum of cats. Both Granit and Müller-Limroth refer to Cajal's [9] and Polyak's [10] histological demonstration of centrifugal fibers. Polyak's investigations on the primate retina are the more pertinent, and are summarized as follows (p. 340): ". . . the only fact positively determined so far is the existence of axon-like fibers and teledendron-like terminations in the retina of the Chimpanzee and that of the Rhesus Macaque, whose continuity with the nerve cells could not be determined. Possibly these are true exogenous or centrifugal fibers arising somewhere in the brain and terminating in the retina. The evidence in support of this is, so far, rather slight." Granit feels that it is too early to suggest a functional role for centrifugal fibers, while Müller-Limroths' interpretation is more positive. Interaction in the contralateral retina cannot be excluded, but its central location is more likely for the following reasons: 1. The centrifugal pathway is still debatable. 2. The FFF is normally determined in the occipital cortex. 3. Central interaction necessarily precedes possible retinal interaction.

As the simplest and most probable situation, it is suggested that the interaction between the elements stimulated by the glare and flicker light source takes place simultaneously in both the right and the left occipital cortex. Of the two stimuli, the glare exposure is incomparably stronger, and, therefore, the interaction is probably unidirectional. The possibility that the direct glare effect on the right eye might be modified by the exposure of the left eye is unlikely, but it cannot be ruled out. Attempts were made to measure the FFF on the right eye under glare, but they were abandoned because glare interfered with the accuracy of measurement.

Bremer [11] found that stimulation of the visual cortex of the cat produces a response in the contralateral cortex, conducted through the corpus callosum, similar to that produced by stimulation of the optic nerve. Thus, interaction between right and left occipital cortex may be additionally involved.

The FFF is related to the time parameter of excitability, particularly the refractory period, as was discussed in an earlier study on the light-dark ratio.[12] Stimulating drugs (amphetamine, caffeine, etc.) increase and depressing drugs (sedatives, alcohol) decrease the FFF (reviewed by Simonson and Brozek [1]). The general effect of glare is that of a depression or inhibition, but occasional stimulating effects also have been observed. The reverse relationship of the contralateral glare effect to the initial FFF is of great interest, because Ukhtomski [13] obtained similar results in his study of intracentral interaction in reflex motor responses. In a state of increased excitability of a motor center, additional afferent stimuli tend to produce inhibition, and the higher the state of excitability the lower is the threshold of the additional stimulus for inhibitory effects. In contrast, at a low excitatory state, additional afferent stimuli tend to produce a stimulation. The demonstration of a similar phenomenon in a visual function suggests that a more general physiological principle may be involved.

Summary

Exposure of the right eye to glare produced a statistically significant drop of the flicker fusion frequency (FFF) of the left eye in three groups of 30 men, tested at three levels of glare (200, 350, and 500 ft-c.). The effect was maximum at 350 ft-c., which is fundamentally different from the direct glare effect. Similar results were obtained in 52 patients with essential hypertension. The variability was large; occasional stimulating effects were noted, and, in some of the subjects, there were pronounced depressions. There was a statistically significant inverse relationship between the magnitude of the control FFF and the glare effect. The possible mechanism of the contralateral glare effect is discussed.

Department of Ophthalmology, Medical School, University of Minnesota (14).

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Conjunctivitis Due to Neomycin Sensitivity

STEPHAN EPSTEIN, M.D., and GEORGE L. McCORMICK, M.D., Marshfield, Wis.

Neomycin is a valuable antibiotic widely used in the topical treatment of infections of the conjunctiva. Until recently neomycin was considered a very rare sensitizer. This, however, is not correct, as neomycin contact dermatitis has been reported by several authors.[1-5] But neomycin contact dermatitis often is masked and overlooked by the physician.[1-3] This also seems to be true when neomycin sensitivity involves the conjunctiva. For this reason, the following four cases are reported.

Report of Cases

CASE 1.—A white man, age 83, was referred by an ophthalmologist because of a conjunctivitis and contact dermatitis of the eyelids. He had used Neo-Cortef eyedrops (hydrocortisone acetate and neomycin sulfate) several months previously because of a conjunctivitis. A few months later, when his difficulty returned, he again used the same eyedrops. This time the conjunctivitis became worse and a dermatitis of the lids developed.

Neomycin sensitivity was suspected.

Patch tests with Neo-Cortef eyedrops, Neo-Cortef ointment and neomycin were negative, but positive intradermal tests with neomycin, 1:1000 and 1:100, proved the neomycin sensitivity.

Both conjunctivitis and dermatitis cleared up after the neomycin-containing eyedrops were discontinued.

CASE 2.—A white boy, 12 years of age, was referred for an allergic investigation because of a conjunctivitis which his ophthalmologist considered allergic in nature. About July 4 the boy had a sore throat; the same day he went water skiing and fell into the water. Subsequently his eyes became inflamed. His physician prescribed eyedrops containing hydrocortisone and neomycin, which seemed to help initially. However, the conjunctivitis never cleared up, in spite of continued therapy, but gradually became worse. Since this condition apparently started with an infection, and since July 4 is not a date for the onset of an allergic conjunctivitis from pollens, other allergic factors were considered and neomycin sensitivity was suspected.

Patch tests with 10% neomycin produced a severe vesicular infiltrated dermatitis. Intradermal tests with neomycin, 1:1000 and 1:100, were strongly positive.

The neomycin-containing eyedrops were replaced by a preparation without neomycin. The conjunctivitis cleared up within the next few weeks and there has been no recurrence to date.

CASE 3.—A 73-year-old woman was referred for an investigation because of an allergic conjunctivitis. She had seen three ophthalmologists, two of whom had prescribed plain hydrocortisone eyedrops and one Neo-Cortef. These latter drops gave her relief initially but after a few weeks the patient noticed an aggravation every time she used them.

An investigation suggested feathers as a major factor of her allergic conjunctivitis; but her history implied additional neomycin sensitivity. Patch tests with a 10% neomycin solution and neomycin-containing preparations were negative. Intradermal tests with a 1:100 solution of neomycin produced a mildly positive reaction. The conjunctivitis responded to antiallergic measures.

CASE 4.—A 48-year-old woman had a conjunctivitis in August, 1955, and also in August, 1957, suggesting weed-senisitivity.

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From the Marshfield Clinic.

Neomycin-containing eyedrops were used and initially gave the patient relief; however, the conjunctivitis never cleared up completely and an acute dermatitis of the eyelids appeared, for which the patient consulted us in November, 1957. Neomycin sensitivity was suspected.

Patch tests were negative, but here, too, intradermal tests with a 1:1000 and 1:100 dilution of neomycin were strongly positive, persisting for over two weeks and also causing a flare-up of the conjunctivitis.

After the neomycin-containing eyedrops were discontinued, the conjunctivitis and dermatitis cleared up rapidly and the patient has since remained well.

Comment

These four cases represent instances of conjunctivitis caused or maintained by neomycin sensitivity. However, this relationship had not been suspected by the attending physicians, except in one instance. There are good reasons for the failure to recognize neomycin sensitivity.

First, neomycin is generally considered to be a very rare sensitizer. This is erroneous. During a period of about two years we have seen over 40 cases of proven contact dermatitis from neomycin.[3] However, in view of the wide use of neomycin, the rate of sensitization is not alarming. Neomycin is still a very valuable topical antibiotic, and the purpose of this paper is not to discourage its use but to make it safer by alerting the ophthalmologist to the occurrence of sensitivity to this drug.

Second, neomycin usually causes a dermal rather than an epidermal sensitivity,* and in the majority of cases of contact dermatitis from this drug, patch tests are negative. This was also the finding in three out of the four cases of conjunctivitis presented above.

Third, when neomycin is used in combination with hydrocortisone the patient may not become aware of an aggravation in spite of existing sensitivity because the immediate beneficial anti-inflammatory effect of hydrocortisone may mask the delayed reaction from neomycin.

In spite of these difficulties, the diagnosis of neomycin sensitivity can be established if the physician becomes aware of such a possibility in prolonged cases of conjunctivitis treated with this drug. Even when patch tests are negative, the allergic sensitization can be proven by intradermal tests with neomycin, which are always positive in cases of contact dermatitis from this drug. Initially 0.05 cc. of a 1:1000 dilution is used, and if this test is negative, a 1:100 dilution is tried. These intradermal tests were also positive in the four cases of conjunctivitis presented in this paper, although the reaction was minor in the one instance where the conjunctivitis was not accompanied by a dermatitis of the eyelids. Since it is known that sensitivity of the mucosa and the skin do not always parallel each other, cases of conjunctivitis due to neomycin sensitivity may be expected where intradermal tests are negative. In such cases, instillation of a neomycin solution in the eye might be the only way to prove the causal relationship. However, the prompt improvement and clearing up of the conjunctivitis where neomycin-containing eyedrops are eliminated constitute satisfactory clinical proof.

Summary

Attention is called to a form of conjunctivitis with or without involvement of the eyelids which is due to allergic sensitivity to neomycin. Such a possibility should be suspected when a conjunctivitis fails to clear up in spite of continued treatment with neomycin-containing eyedrops.

Patch tests for neomycin sensitivity are often negative, but the allergic nature of the reaction usually can be demonstrated by appropriate intradermal tests.

Awareness of the possibility of allergic sensitivity to neomycin will permit the physician to continue with safety the topical use of such a valuable antibiotic.

Marshfield Clinic.

* Peculiarities of neomycin sensitivity have been discussed by one of us (S. E.) elsewhere.[1-3]

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The Scleral Buckling Procedures

III. Technical Difficulties of Reoperations

R. J. BROCKHURST, M.D.; C. L. SCHEPENS, M.D., and I. D. OKAMURA, M.D., Boston

In the first article of this series we have described four basic types of scleral buckling and outlined the pre- and postoperative care of a standard case. In the second article we have discussed the management of the more frequent technical difficulties which may develop in a primary scleral buckling operation. The present article deals with some of the special obstacles often encountered when a scleral buckling is performed as a reoperation. It is divided into four parts: The first part analyzes problems during reoperations which follow any type of retina surgery; the second part refers to special difficulties developing after retinopexies; the third part is devoted to problems created by previous scleral resections, and in the fourth part the consequences of large perforations are discussed. Techniques used in reoperations following a scleral buckling will be described in our next article.

1. Difficulties During Reoperations Which Follow Any Type of Retina Surgery

The problems which may arise when a scleral buckling is performed after any type of unsuccessful retina surgery concern the conjunctiva, the securing of proper exposure, the sclera, the vortex veins, and the tying of sutures.

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From the Retina Foundation, Department of Ophthalmology of the Massachusetts Eye and Ear Infirmary and Harvard Medical School.

Conjunctiva.—In a reoperation it is particularly important not to make the peritomy too close to the limbus, because this interferes with the pericorneal circulation and may damage the aqueous veins. As a rule, the incision should either coincide with that of the previous operation or it should be parallel and more posterior to it.

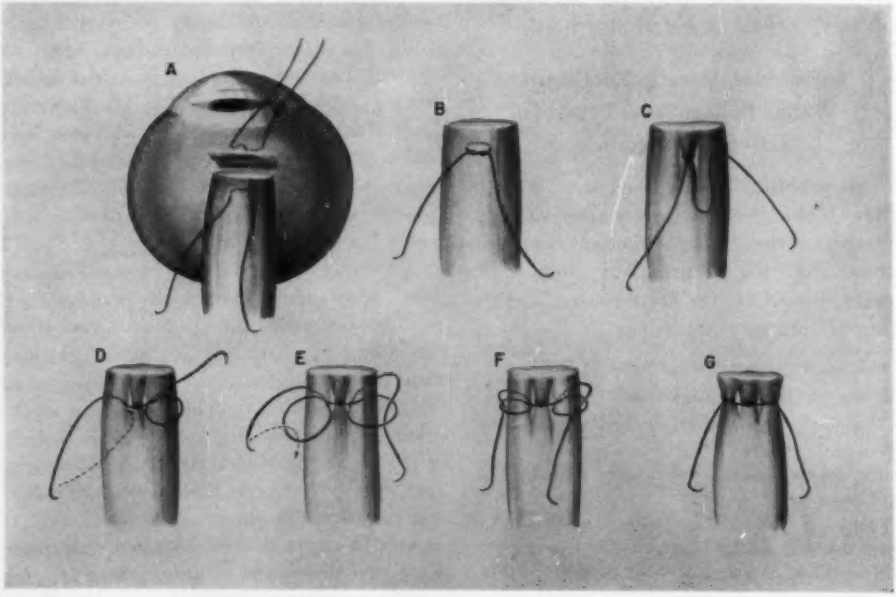
The conjunctiva may be affected by symblepharons, granulations, and dense adhesions to the sclera. Postoperative symblepharons may be present either as narrow bridges or as dense broad adhesions. They are generally severed at the time of reoperation, and in so doing it may be necesary to repair the tarsal and bulbar conjunctiva at the end of the procedure. Granulation tissue in the conjunctival sac results from subconjunctival proliferation through the conjunctival wound of a previous operation. These granulations should be excised carefully after the conjunctiva has been reflected. Excessive bleeding from the pedicle of a granuloma is controlled by diathermy coagulation. Dense adhesions with excessive amounts of scar tissue may exist between conjunctiva and sclera. These adhesions should be severed by careful dissection with curved pointed scissors.

Securing of Proper Exposure.—Deep orbital tissue should be cut with curved pointed scissors and under direct observation. Blind spreading of orbital tissues in reoperations may cause a perforation of the sclera in an area which is thin or which has been weakened by previous diathermy. The densely scarred subconjunctival tissues contain many fine blood vessels which bleed profusely during the exposure stage of the operation. It is best to excise this vascularized scar tissue by sharp dissection. The assistant is very

important, for he must constantly sponge the field; cotton tip applicators, used as sponges, have been found to be most satisfactory. After the scar tissue has been removed, a few vessels may be found on the surface of the sclera or perforating through it; these are obliterated with light diathermy. Diffuse bleeding from soft orbital tissues is annoying because there seems to be no effective way to control it. In such cases it is helpful to continue dissecting in an area where there is less bleeding. After some time the diffuse type of bleeding stops spontaneously and allows easier completion of the dissection.

A major problem in the exposure stage of a reoperation is the identification and detachment of the recti muscles. Generally, muscles located in an area previously operated on are embedded in thick white scar tissue which may be mistaken for the muscle itself. This scar tissue should be excised until the muscle tendon is found. It is helpful to place a 0000 nonabsorbable surgical (silk) traction suture in the sclera anterior to the expected location of the tendon. When the sclera appears considerably damaged by previous surgery, the traction sutures are inserted with a very sharp needle, such as a Grieshaber needle No. 82/7. This suture allows the assistant to rotate the eye, thereby improving exposure. Once the tendon is found, scar tissue on either side is separated from it by dissection with pointed scissors. No muscle hook is used in attempting to isolate muscles located in areas where previous surgery has been performed, as there is a great risk of perforating the sclera. Instead, it is preferable to sever the muscle tendon near its scleral attachment before placing a 00000 plain absorbable surgical (gut) suture in the tendon. As persistent bleeding from the detached muscle is very frequent in reoperations and is a source of annoyance during the whole procedure, it is useful to tie the

Fig. 1.—Method of passing 00000 plain gut suture through a muscle which is bound down to the sclera. Note the 0000 silk traction suture which is placed in the sclera before detaching the muscle. *A*, the muscle is detached from its tendon, and a double-armed gut suture is passed through its middle third; care is taken not to damage the dorsal vessels of the muscle. *B*, a single knot is tied. *C* and *D*, each needle is passed through and then looped around the outer third of the muscle. *E* and *F*, the gut suture is locked around the outer third of the muscle. *G*, the gut suture is finally pulled up.



gut suture around the muscle, as indicated in Figure 1. The muscle is then carefully dissected off the sclera with pointed scissors, and this should be done under direct visualization.

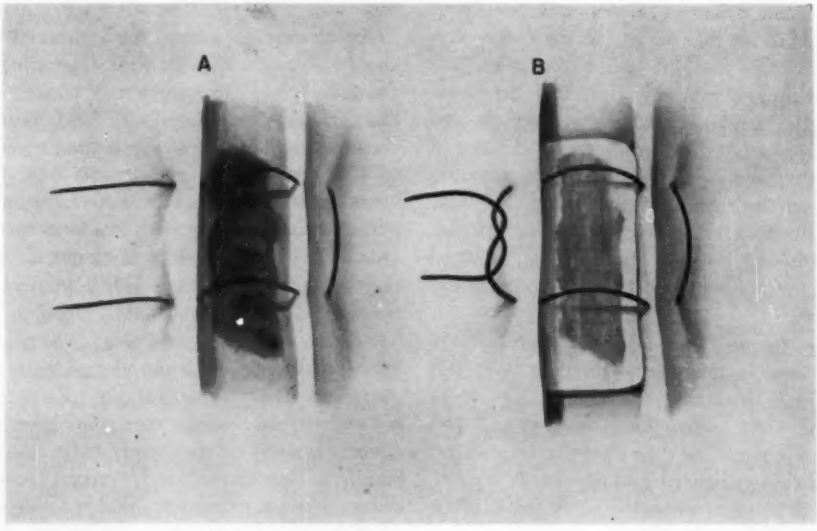
The flat tendons of the oblique muscles are often difficult to dissect off the sclera. When exposure requires it, one-third of their scleral insertion may be severed without resuturing it to the globe at the end of the operation. If about one-half or more of the tendon has to be severed, it is advisable to reattach it to the scleral stump with a 00000 gut suture. It is important to remember that the point of emergence of a vortex vein is always hidden under the temporal portion of the superior oblique tendon.

Adequate exposure must be secured without raising the intraocular pressure, for a high ocular tension increases the danger of rupturing the globe. Therefore, excessive traction on the globe should be avoided by detaching two, sometimes three, and rarely four recti muscles, as required. For the same reason, it is wise to incise the conjunctiva and dissect the scar tissue from the sclera over a much larger area than that of the planned operation. As an example, if the operation is to be done in one quadrant, the adhesions are dissected free in one additional quadrant on either side, thus making a total of three quadrants.

Sclera.—All scar tissue must be excised from the surface of the sclera. After satisfactory exposure is obtained, the sclera is inspected for weak areas which might perforate during subsequent manipulations. Excessively thin sclera, and that which has been previously treated with strong diathermy, is prone to rupture and may have to be reinforced, as indicated in Figure 2.

Two difficulties are likely to occur when retinal breaks are localized with a diathermy mark.[1] First, the weakened sclera may be perforated with the localizing electrode. Second, it may be found that no mark from the localizing electrode appears in the fundus even though the retina is in contact with the choroid during the localization. This is generally due to the presence of scar tissue on the surface of the sclera or to an edematous sclera. It is, therefore, important to

Fig. 2.—Method for protecting a necrotic area in the bed of the lamellar scleral resection. *A*, a mattress suture is placed over the necrotic area, and, in this case, the edge of the scleral resection must be grasped with toothed forceps when the suture is passed through the sclera. *B*, a polyethylene sheet of proper size and 0.0015 in. thick is placed under the mattress suture. The mattress suture is pulled up as soon as it is possible to do so without raising excessively the intraocular pressure.



remove all scar tissue from the sclera and to keep the area dry during the diathermy applications.

After the localization of breaks, the area to be buckled is determined. The buckle is planned so that the breaks will fall on its anterior slope.[1] In reoperations, the proposed area to be buckled is frequently scarred by previous diathermy. As a result, the sclera is often very weak in spite of its greatly increased thickness due to edema. In order to obtain effective diathermic coagulation of the underlying choroid, it is necessary to excise the greatest portion of the scleral thickness. It is extremely difficult to judge the thickness of edematous sclera, since it is more transparent than normally, regardless of its increased thickness. As a consequence, the bluish color of the choroid may show through edematous sclera when there is still a thick layer of this tissue. Further excision must then be done, with the utmost care, to insure adequate coagulation of the underlying choroid. It is wise to excise only a short lamella of sclera at a time, measuring no more than about 10 mm. long, and immediately after excision to place a 0000 black silk mattress suture in the usual manner. Then another 10 mm. section may be excised, and so on. All scar tissue must be removed from the portion of the sclera where the mattress suture will be placed. Failure to do this results in the suture cutting through the soft scar tissue when it is pulled up and tied. If, after lamellar resection, the remaining sclera is necrotic and thin, it is advisable to place a small piece of polyethylene sheet under the mattress sutures on the weakened area (Fig. 2). This sheeting serves as a temporary reinforcement during the operation and is removed when the polyethylene tube is placed under the sutures.

One frequent reason for failure of reoperations is that the diathermy does not effectively coagulate the choroid, as it is applied over edematous, thickened, and necrotic sclera. The type of electrode selected for applying diathermy to previously treated sclera is of great importance. A flat-surface electrode may cause surface desiccation, with the resulting effect that necrotic sclera may stick to the electrode, which thereby tears off large areas of sclera and exposes bare choroid. The same complication may also occur when the blunt point electrode[1] is used. When the sclera is necrotic, it is advisable to make careful applications with a fine needle electrode[1] which is applied gently and obliquely against the thinned sclera. The electrode tip is held at an angle of approximately 45 degrees to the surface being treated. When the sclera is very thin, the current should be reduced from that used conventionally, for the thinner sclera may be perforated if the current is too intense. It is a good plan to apply diathermic treatment in small zones at a time, as this results in only a slight elevation of the intraocular pressure. If a large area is treated at one time, the intraocular pressure may rise to a point where rupture of the globe is more likely to occur. Diathermy is applied in the area of the lamellar resection immediately after placement of one or two mattress sutures. The resection is then continued for a short distance; another suture is placed; additional diathermy is applied, and a protective polyethylene sheet is used if necessary. If this program is followed, the danger of perforating the globe is minimized.

No attempt to release the subretinal fluid should be made without first examining the fundus. In an area previously treated with diathermy, it is common to find localized chorioretinal adhesions, corresponding either to strong diathermy applications or to previous perforations. If, at reoperation, a perforation is inadvertently made in such an area, no subretinal fluid will escape; instead, the retina will be incarcerated in the perforation and vitreous may be lost.

Vortex Veins.—There are two reasons why interference with the vortex veins is a great problem in reoperations. First, it is not known how many vortex veins have been either damaged or completely obliterated by previous operations, and, second, vortex veins are often extremely difficult to identify

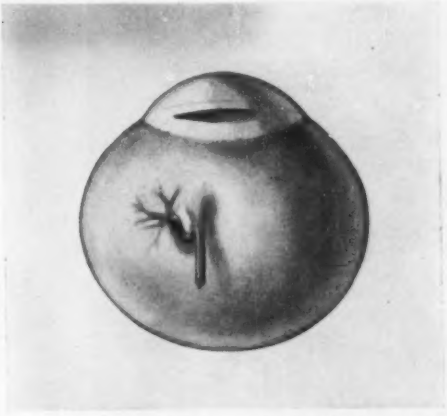


Fig. 3.—Scar tissue around the globe may pull a vortex vein sideways, forward, or both.

in scar tissue. Dissection should be particularly careful in the location where their point of emergence is likely to be found, that is, on either side of the superior and inferior recti muscles 14 mm. to 22 mm. from the limbus. The orbital portions of the vortex veins normally lie in loose areolar tissue and are, therefore, easy to identify in primary operations. In reoperations retracting scar tissue may pull the veins into abnormal loops, and not infrequently such loops run anteriorly (Fig. 3). If a vortex vein is torn or cut accidentally, it is probably best to let it bleed, as its coagulation stops external bleeding but may cause an intraocular hemorrhage. The bleeding point is useful to mark the location where the vortex vein emerges from the sclera. It is essential not to prick or cut into the intrascleral course of the vein or into the ampulla, since this may cause severe intraocular hemorrhage. If a vortex vein is not found when reoperation is being done, a choroidal perforation for the release of subretinal fluid should never be made in the meridian of its normal location, as the vortex ampulla or one of its large channels may be perforated.

Suture Tying.—Mattress sutures tend to cut through edematous sclera when they are pulled up, and this difficulty is avoided by the use of polyethylene plates.[2] If excesive tension is created when the circling suture is pulled up, and necrotic sclera is present under the circling tube, there is danger of rupturing the globe, with the result that the polyethylene tube may enter the subretinal space. Rupturing of the globe in this manner occasionally occurs after an otherwise uneventful operation, and it is practically always followed by failure of the retina to reattach. To avoid this complication, the circling suture must be pulled up gently, the intraocular pressure must be constantly checked by indenting the cornea with a muscle hook while adjusting the circling suture, and the fundus must be frequently examined with an ophthalmoscope.

Reattaching the extraocular muscles to weakened edematous sclera may prove difficult and should be done with great gentleness. The use of sharp needles which can be passed easily through the sclera decreases the incidence of complications. It has been found advisable to use von Pirquet's method[3] of reattaching extraocular muscles. With each end of the 00000 gut suture, this author makes two bites in the sclera, near the stump of the detached muscle (Fig. 4). This ensures a better anchorage in edematous tissue; it also prevents slipping of the muscle before the knot is tied, thus avoiding the need for an assistant to hold the muscle in place.

2. Problems During Reoperations Which Follow Retinopexies

Special problems sometimes encountered when a scleral buckling is performed after an unsuccessful retinopexy may result from excessive diathermy and from multiple scleral perforations.

Excessive Diathermy.—Intense surface diathermy applications cause necrosis of the sclera, which is repaired by proliferation of episcleral tissue. In view of this, scar tissue must be dissected off the sclera with great care when reoperation is being performed, since bare atrophic choroid may be exposed. Should this occur, the bulging choroid must be reinforced by a sheet of polyethylene held in place with a mattress suture (Fig. 2).

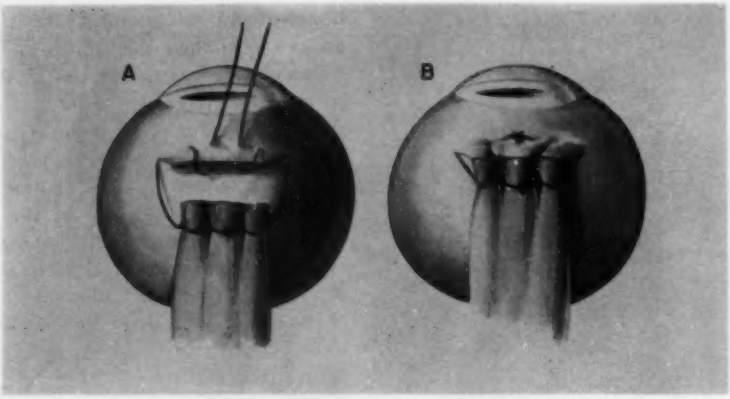


Fig. 4.—Von Pirquet's method for resuturing the detached muscle. *A*, the gut suture is passed through the sclera at both ends of the muscle stump. A second bite is made in the sclera to prevent the suture from slipping. *B*, the reattached muscle may be recessed to a variable degree, depending on the indications present.

Because of the location of previous diathermy, the area to be buckled may be bounded by necrotic sclera either anteriorly or posteriorly or on both sides. In such instances, it is mandatory to use polyethylene plates in order to prevent cutting out of the mattress sutures.[2] Intense surface diathermy applications may cause localized necrosis of the retina, with formation of irregular retinal breaks. In a reoperation, such breaks should, as far as possible, be placed on the anterior slope of the scleral buckling. They are always difficult to detect with the ophthalmoscope, as they occur in areas where the choroid and retina have atrophied after the diathermy applications. The color contrast between the retinal break and the surrounding retina is, therefore, almost absent.

Multiple Scleral Perforations.—After a retinopexy where numerous perforations were made, such as may result from the use of Walker pins, several difficulties generally occur at reoperation. The dissection of episcleral tissue over former areas of perforation may cause escape of subretinal fluid; the same may happen in dissection of the scleral lamella. The resulting softness of the globe makes the performance of scleral buckling rather difficult. If there is considerable loss of subretinal fluid, excessive hypotony follows, and this increases the danger of intraocular hemorrhage. Drawing up the mattress sutures which are already in place may help to reestablish a normal intraocular pressure. When necessary, the accidental perforation is closed with a mattress suture under which a polyethylene sheet is placed (Fig. 5). This mattress suture may be pulled up temporarily and locked to close the perforation. At a later stage of the operation, more subretinal fluid may be allowed to escape through the accidental perforation, and this often eliminates the necessity of making a deliberate perforation of the globe for the release of subretinal fluid.

Multiple perforations of the globe, performed at a previous unsuccessful operation, frequently result in multiple retinal breaks. These are difficult to see for three reasons. First, the breaks themselves are generally pinpoint in size; second, the diathermized retina which surrounds them is very thin, and, third, the diathermized choroid behind the breaks is atrophic. Often it is possible to place the scleral buckling either over these breaks or between the breaks and the disc, thus creating a barrage. When the breaks lie so far posteriorly that they cannot be treated by the usual buckling operation, they are covered by an additional trap door operation.[2]

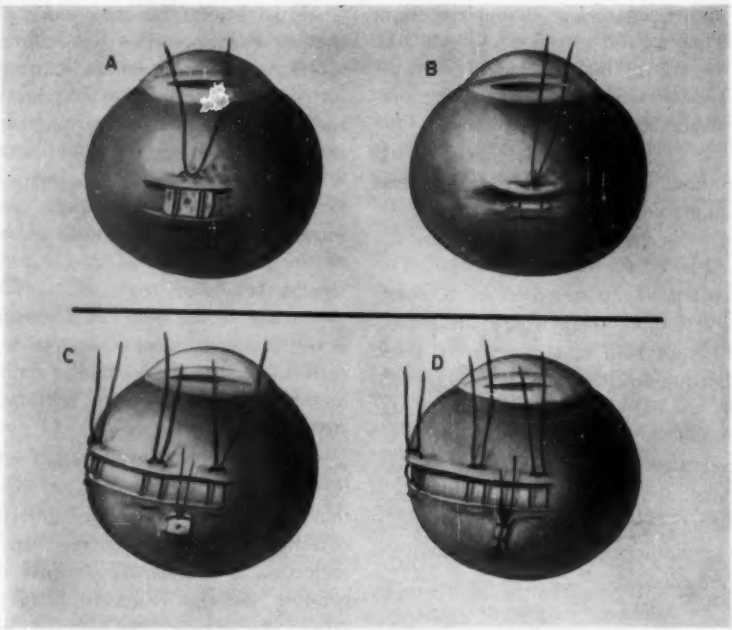


Fig. 5.—Control of premature loss of subretinal fluid. *A* and *B*, when the lamellar scleral resection involves a previously treated area, an old perforation may cause premature escape of subretinal fluid. This is corrected by a mattress suture placed as shown and a small sheet of polyethylene 0.0015 in. thick under the suture. The perforation is closed by pulling up and locking the mattress suture. *C* and *D*, if the premature loss of subretinal fluid occurs outside the area to be buckled, it is closed by the same method. In both cases additional subretinal fluid can often be released from the point of accidental perforation, when the scleral buckling sutures must be pulled up. This avoids the necessity of perforating the globe elsewhere. When a sufficient amount of subretinal fluid has escaped, the suture which has been placed over the perforation is tied.

3. Problems During Reoperations Which Follow Scleral Resections

There are two special problems which may develop when a scleral buckling is performed after an unsuccessful scleral resection. The first is exposure of thinned-out sclera, and the second is the difficulty of performing a scleral buckling in the immediate vicinity of a previous scleral resection.

Exposure of Thinned-Out Sclera.—After a scleral resection, the sutures used to close the resection may have pulled out, exposing thinned sclera. This occurs mainly when diathermy has been placed on either side of the area of resection, thus weakening the sclera with resultant pulling out of sutures. When such an area is found during reoperation, it is mandatory to support it. A weak zone of small size is repaired with a single mattress suture, and, when the eye is soft, this suture is pulled up, thus creating an infolding. If the area is large, several mattress sutures are necessary, and a polyethylene sheet can be placed under the sutures as a reinforcement.

Buckling Close to Previous Resection.—When the scleral buckling must be performed in the neighborhood of a previously performed scleral resection, four possible relationships may occur between the previous resection and the planned buckling. First, the scleral buckling may be over the area previously resected; second, the scleral buckling may be anterior or posterior to the resection but adjacent to the line of the resection closure; third, the scleral buckling may be posterior to the resection with 3

mm. or more separating its anterior limit from the line of the resection closure, and, fourth, the scleral buckling may cross the area of resection, usually because the previous resection was not made parallel to the limbus.

In the first situation, where the scleral buckling must cover the area which had already been resected, care must be exercised in order to avoid rupture of the globe. The sclera is often irregular in thickness, being abnormally thin in areas where the scleral sutures did not hold and excessively thick where the previous scleral resection was adequately closed. The operation should be done in small steps, as described earlier in this article. Previous sutures should be removed; small areas of scar tissue and sclera excised, new 0000 black silk mattress sutures placed, and diathermy applied without perforating the choroid.

When the buckling procedure must be done either anterior or posterior to the resection but adjacent to the line of resection closure, the original resection should not be opened, since unnecessary risk is then involved. Therefore, as the new lamellar scleral resection is performed, the old sutures are removed and new sutures are placed to include the old resection (Fig. 6*A*).

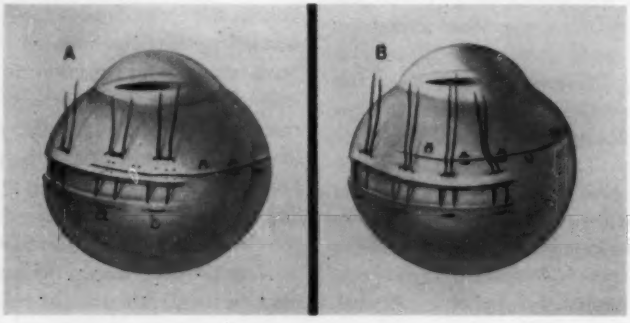
If the scleral buckling must be done 3 mm. or more posterior to the line of a previous resection, the operation is performed as usual (Fig. 6*B*). The old resection should not be disturbed, since no treatment is indicated in that area, and any dissection there will only serve to weaken the sclera, with possible rupture of the globe and loss of intraocular contents. Loose scleral sutures of the previous operation are removed. It should be noted that scleral buckling is practically never done in a location which is considerably anterior to a previous scleral resection because the latter is almost always located between the ora serrata and the equator.

A final word should be said about a scleral buckling which crosses an old resection so that part of the buckle lies anterior to the resection and part is posterior. In this case, each area is handled as outlined above, depending on the relationship between the scleral buckling and the resection in any one given zone.

4. Difficulties During Reoperations Which Follow Large Perforations

Unusual difficulties may occur when a scleral buckling is performed after an unsuccessful surgical procedure during which

Fig. 6.—Scleral buckling located close to a previous resection. *A*, when the scleral buckling is adjacent to a previous lamellar resection, the old resection should not be disturbed. The new mattress sutures (*a* and *b*) must include the anterior lip of the previous scleral resection. Old sutures are removed in the area of the new resection. The undisturbed sutures of the previous resection, to the right of the new resection, have partially pulled out of the sclera, and as a result, they are not in a straight line. Such loose sutures may be removed. *B*, when the scleral buckling is at least 3 mm. away from a previous resection, the buckling is done as if no resection were present. Scleral sutures of the previous operation are removed when they are found to be loose.



large perforations of the globe were done. These large perforations may be divided into two categories: first, moderate-size openings resulting from the use of a diathermy point of large diameter or from that of an injection needle of gauge 18 to 20 and, second, very large openings which may have occurred either accidentally during a previous operation or from a deliberate perforation as is sometimes done with a trephine or a Graefe knife.

Moderate-Size Perforations.—Such perforations of the globe are sometimes made either for the release of subretinal fluid or for the injection of foreign material into the vitreous cavity. As a rule, they are complicated by the development of connective tissue proliferation into the vitreous cavity. When the perforation is made in the vicinity of the pars plana ciliaris, the intraocular proliferation may cause considerable haze all around the periphery of the vitreous, thus making examination of this portion of the fundus more difficult than usual. As this proliferation often extends all around the vitreous base before it invades the posterior portion of the vitreous cavity, it may remain undiagnosed for a long time. When the site of a moderately large perforation is examined with the ophthalmoscope, a mushroom-like whitish elevation of variable size is often visible on the inner surface of the retina, due to the intraocular proliferation of connective tissue. The top of the mushroom is somewhat hazy, and fine whitish strands may be seen radiating from it into the vitreous cavity. The retina is adherent to the site of perforation; when it is detached around this site, it forms fixed folds radiating from the perforation.

If the perforation is in the area of the pars plana ciliaris, it is generally advisable to extend the scleral buckling to the quadrant in which the perforation is found, but it should be placed at or near the equator of the globe. When the perforation is near the equator, the scleral buckling should be so located that the perforation is on its anterior slope. A mattress suture is placed over the perforation immediately after the parallel incisions are made in the sclera and before the scleral flap is dissected. As a rule, dissection of the sclera should be performed all around the perforation but should not extend over the perforation itself. Premature escape of subretinal fluid and vitreous loss through the perforation site is prevented by drawing up the mattress suture.

In the event that the perforation is very posterior and the scleral buckling must be placed anterior to it because of the location of retinal breaks, two special cases should be considered. First, the perforation may reopen in the course of the dissection, and subretinal fluid or vitreous may escape. This is stopped by placing a 0000 black silk mattress suture over the scleral perforation (Fig. 5*C* and *D*). The second possibility is that the perforation may be associated with a retinal break. In this case, a trap-door procedure must be performed posterior to the main scleral buckling.[1] It may be felt that a trap-door procedure would be hazardous because of the risk of reopening the large perforation, incarcerating the retina and losing vitreous. In this case, a short scleral buckling without excision is advisable.[1]

Very Large Perforations.—Very large perforations of the sclera and choroid may exist as a result of an accidental rupture during previous surgery, of trephining, or of some other similar method for the release of subretinal fluid. Such methods are definitely inadvisable, as frequently they cause incarceration of the retina, considerable vitreous loss, and vitreous hemorrhage. Very large perforations are easily diagnosed with the ophthalmoscope by the existence of a large star-shaped retinal fold, at the center of which the choroid is absent, showing the glistening white of the sclera. From this white center a number of gray streaks fan out in the vitreous cavity and represent the intraocular fibroblastic proliferation. The vitreous is generally hazy and shows the remnants of a hemorrhage. During surgery, the area corresponding to any such opening should be carefully exposed and the sclera examined. If there

seems to be a danger of rupturing, a mattress suture is placed over the area and a polyethylene sheet is used as reinforcement under the suture. If the buckling must cross such a perforation, extreme caution is necessary. To diminish the danger of a new vitreous loss, no sclera should be excised in the immediate vicinity of a very large perforation. For the same reason, no attempt should be made to release subretinal fluid in this area.

Summary

A description is made of the technical difficulties which arise when a scleral buckling operation follows unsuccessful retina surgery of another type.

Five difficulties are likely to be encountered during reoperation after any type of retina surgery. First, the conjunctiva may be adherent to the sclera and may show symblepharons and granulomas. The second problem is that of securing proper exposure, which is obtained by careful dissection and by detaching recti muscles whenever indicated. The third difficulty is related to the sclera, which is often friable and edematous, rendering diathermy applications less effective and more difficult. The fourth is the identification of the vortex veins, and the fifth problem is related to the placement and tying of scleral sutures.

Following retinopexies, special difficulties at the time of reoperation result from excessive diathermy applications and from multiple scleral perforations. After scleral resections, thinned out sclera may be exposed, and it may be difficult to perform a scleral buckling in the immediate vicinity of a previous resection. Finally, special problems caused by the existence of large scleral perforations are discussed.

99 West Cedar St. (14).

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Penetration of Penethamate, a Penicillin Ester, into the Tissues of the Eye

G. M. BLEEKER, M.D., and E. H. MAAS, M.D., Amsterdam, Netherlands

If antibiotic treatment of an inflammation of the eye or of the adnexa is to be successful, the micro-organisms involved must be susceptible to the antibiotic, while the concentration of the latter at the site of the infection must be sufficient.

Superficial infections of the eye are effectively dealt with by the local application of antibiotics. The local concentration can easily be maintained at an effective level and microbiological identifications will make it possible to choose from the many antibiotics available.

Treatment of infections of the inner eye offers no such opportunities. As long as the material remains hidden in the inner tissues of the eye, bacterial identification will be impossible. Apart from this, it is a well-established fact that it is very difficult to bring antibiotics into the inner eye in adequate quantity. Penicillin and streptomycin, given by subconjunctival injections, are favorable exceptions.[1] But when it is necessary to rely on the blood stream, chloramphenicol is the only antibiotic that reaches the vitreous body in sufficient quantity.

Penicillin is slow to pass the barrier that separates the inner eye from the blood. Only when the blood level is very high do concentrations of therapeutic value appear in the anterior chamber.

In investigation of other antibiotics that might be able to pass from the blood into the inner eye, attention was drawn to penethamate, a penicillin ester. Penethamate * is the hydroiodide of the diethylaminoethyl ester of penicillin. After dissolution in water slow hydrolysis occurs, resulting ultimately in the release of penicillin. So far, there is a resemblance to the well-known procaine penicillin, which is also slowly split up into its original components by hydrolysis. There are, however, differences.

Dragsted and his associates were able to demonstrate that parenteral injections of the penicillin ester resulted in a more substantial penicillin level in the tissues of a lung than a comparable dose of procaine penicillin. On the other hand, the concentrations in the blood after procaine penicillin exceeded those of the ester.[6-7]

Further evidence was given by Goslings et. al., who were not only able to confirm these facts, but also to find increased concentrations in other organs.[8]

A more striking illustration was provided by Gylfe, Bayne, and Boger in their studies on the penetration into the cerebrospinal fluid.[9] Parenteral injections with the ester resulted in effective levels of penicillin in the vast majority of their cases, whereas the controls, treated with procaine penicillin, uniformly failed to show any appreciable amount in the spinal taps.

As the inner tissues of the eye are separated from the blood by a barrier, similar to the blood-fluid barrier, experiments were carried out to compare the penetration of penicillin into the eye after parenteral administration of penethamate and procaine penicillin.

Technique

Samples of blood, aqueous, and vitreous were obtained by means of punctures from the eyes of living rabbits. Where possible, superficial anesthesia was used. Precautions were taken to avoid contamination of the

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* Penethamate is commercially known as Leocillin (Denmark), Estopen (Britain), Bronchocillin (France), Deripen (Netherlands), Pulmo 500 (Germany), and Toraxilina (Spain).

aqueous and vitreous humor with blood. In those cases where the concentrations in all the tisues of the eye were estimated, the eye was enucleated under local anesthesia and immediately frozen in solid carbon dioxide. The compounds were dissected from the still-frozen eye at a temperature below freezing.

Penicillin concentrations in the extracts were measured according to the microtest of Goslings, which is based on inhibition of the growth of Streptococcus (Type A Lancefeld) in serial dilution.[18] As in other experiments with antibiotics, there is always considerable variability in the outcome of the estimates. These can be attributed to shortcomings in the technique of administration and the method of analysis. Where these errors have been eliminated as far as possible, there still remain the variable individual reactions of the test animals. To reduce these variations, the left eye of the rabbit was always used for the experiment with procaine penicillin, while a fortnight later the right eye was used for a similar experiment with penethamate. Never was one eye used for more than one experiment.

Where "average" is mentioned in the tables, no attempt is made to achieve mathematical accuracy. For that, the number of experiments is too small. Conclusions are drawn only when the difference in the outcome of the estimates was constant and evident.

TABLE 1.—*Distribution of Procaine Penicillin and Penethamate in the Aqueous and Vitreous of the Eye of the Rabbit After Intramuscular Injection of 100,000 Units. Data Represent Units Per Milliliter*

Hrs. After Injection	Procaine Penicillin, Units/Ml.			Penethamate, Units/Ml.		
	Blood	Aqueous	Vitreous	Blood	Aqueous	Vitreous
	8	0.25	0.016	6	0.5	0.5
2	3	0.5	<0.01	8	0.38	0.5
	8	0.08	<0.005	6	0.5	0.25
	8	0.125	<0.005	4	0.375	0.25
Av.	7	0.24	<0.01	6	0.44	0.38
	4	0.19	<0.01	1.33	0.33	0.125
3	3	0.125	<0.01	8	0.16	0.25
	5.3	0.25	<0.005	6	0.5	0.125
	4	0.25	0.01	3	0.75	0.5
Av.	4	0.20	<0.01	4.6	0.44	0.25
	6	0.125	<0.008	0.37	0.19	0.37
	10.7	2.67	0.04	1.5	0.19	0.25
4	8	0.67	0.01	0.5	0.25	0.5
	8	0.75	0.008	0.12	0.16	0.33
Av.	8.2	1.05	0.015	0.62	0.20	0.36
				1.5	0.5	0.19
6				0.19	0.03	0.5
				0.25	0.125	0.375
				0.375	0.125	1.0
Av.				0.58	0.2	0.51
	0.08	<0.005	<0.005	0.75	0.25	0.375
8	0.03	<0.005	<0.005	0.03	0.03	0.18
	0.06	0.01	<0.005	0.02	0.03	0.25
	0.06	0.01	<0.005	0.05	0.05	0.25
Av.	0.04	<0.01	<0.005	0.21	0.09	0.26
				<0.008	<0.008	0.03
14				<0.008	<0.008	0.03
				<0.008	<0.008	0.03
				<0.008	<0.008	0.04
Av.				<0.008	<0.008	0.04

Results

The results are given in Table 1. These figures make evident the following information.

I. The values obtained in the blood after procaine penicillin injections are superior to those obtained with penethamate, although the latter are more prolonged. Both values coincide with data provided by others.[6,8]

II. The concentrations in the aqueous humor are of the same magnitude. After eight hours, however, the concentrations are greater with penethamate.

III. The penicillin levels in the vitreous humor after procaine penicillin are negligible, a result which is in striking contrast to the result of the administration of penethamate. As early as two hours after injection of the ester, the concentrations in the vitreous amount to an effective level (0.38 units per gram). From the fourth hour after injection, these levels exceed those in the anterior chamber and in the blood, and it is only after 14 hours that their therapeutic value becomes doubtful.

From these figures it is evident that an intramuscular injection of 100,000 units of penethamate provides penicillin levels of therapeutic value in the vitreous of the rabbit.

This does not necessarily imply that the human eye follows the same pattern. In

these experiments the penicillin blood level, for instance, mounted up to 7 units per cubic centimeter. Goslings and co-workers obtained only 1.25 units per cubic centimeter in human blood one hour after an intramuscular injection of 500,000 units of penethamate.[8]

To make a forecast of any value for the human eye it was necessary to repeat the experiments with rabbits with a smaller dose, in order to make new evaluations of the vitreous at a moderate blood level. Table 2 gives the result of an intramuscular injection of 10,000 units of penethamate, or one-tenth of the dose previously used. To facilitate comparison, the results of injections of 100,000 units of penethamate and 100,000 units of procaine penicillin, administered under the same conditions, are added.

Two hours after the injection of 10,000 units of penethamate, the penicillin concentration in the vitreous is of therapeutic value (0.09 units per cubic centimeter) and remains so until the fourth hour. Since these results were achieved at a modest level in the blood of a rabbit (0.38 units per cubic centimeter), penethamate may be expected to provide a useful concentration in the human vitreous. Goslings and Hers were easily able to obtain a more substantial level (1.25 units per cubic centimeter) in human blood.

TABLE 2.—*Distribution of Penicillin in the Aqueous and the Vitreous of the Eye of the Rabbit Two and Four Hrs. After Intramuscular Injection of 100,000 Units and 10,000 Units of Penethamate, and of One Hundred Thousand Units of Procaine Penicillin*

	2 Hrs. After Intramuscular Injection, Units/Gm. of Wet Tissue			4 Hrs. After Intramuscular Injection, Units/Gm. of Wet Tissue		
	Blood	Aqueous	Vitreous	Blood	Aqueous	Vitreous
Penethamate 100,000 Units						
	6	0.5	0.5	0.37	0.19	0.37
	8	0.38	0.5	1.5	0.19	0.25
	6	0.5	0.25	0.5	0.25	0.5
	4	0.38	0.25	0.12	0.16	0.33
Av.	6	0.44	0.38	0.6	0.20	0.36
Penethamate 10,000 Units						
	0.09	0.03	0.06	0.01	0.02	0.03
	0.09	0.03	0.09	<0.008	<0.008	0.05
	0.67	0.047	0.08	<0.008	<0.008	0.02
	0.67	0.08	0.13	<0.008	<0.008	0.04
Av.	0.38	0.04	0.09	<0.008	<0.008	0.03
Procaine Penicillin 100,000 Units						
	8	0.25	0.02	6	0.13	<0.008
	3	0.5	<0.01	10.7	2.67	0.04
	8	0.08	<0.005	8	0.67	0.01
	8	0.13	<0.005	8	0.75	0.01
Av.	7	0.24	<0.01	8.2	1.05	0.015

TABLE 3.—*Penetration of Penethamate into the Tissues of the Eye of the Rabbit* *

	Penethamate, Units/Gm. of Wet Tissue				
	Rabbit 1		Rabbit 2		
	R. Eye	L. Eye	R. Eye	L. Eye	Av.
Cornea	0.09	<0.09	0.22	0.17	0.12
Aqueous	0.03	0.03	0.04	0.08	0.04
Anterior uvea	1.14	1.31	6.7	6.15	3.8
Lens	<0.017	<0.016	<0.01	<0.009	<0.01
Vitreous	0.063	0.09	0.08	0.13	0.09
Posterior uvea	0.27	0.27	1.88	4.86	1.82
Sclera	0.15	0.36	0.58	0.48	0.39
Blood	0.09	0.09	0.67	0.67	0.38

* Penethamate, 10,000 units had been injected intramuscularly two hours previously.

In the previous experiments the results of the administration of penethamate were estimated in the blood, in the aqueous, and in the vitreous only. It may also be of interest to show the concentrations in the other tissues of the eye.

Considering the small initial dose of 10,000 units (i. m.) and the low level in the blood (0.38 units per cubic centimeter), the values in the iris and the ciliary body (anterior uvea), and in the chorioid and the retina (posterior uvea) are remarkable; they exceed the blood level many times. Evidently these tissues have a certain affinity to the penicillin ester. The cornea and the sclera have a sufficient share, and the lens contains only traces.

The previous experiments suggest that penethamate easily penetrates the barrier that separates the blood and the inner tissues of the eye and that, in this respect, it is far superior to procaine penicillin. Avoiding the barrier by the subconjunctival route (Table 4), penicillin is known to penetrate into the eye to a very high degree by direct diffusion through the sclera. It was deemed of interest

TABLE 4.—*Distribution of Penicillin in the Tissues of the Eye of the Rabbit After Subconjunctival Injection* *

	Units/Gm. of Wet Tissue									
	Procaine Penicillin, 150,000 units					Penethamate, 75,000 units				
	1†	2	3	4	Av.	Av.	1	2	3	4
Cornea	0.84	3.4	0.75	12.6	4.4	<0.07	<0.1	<0.068	<0.06	<0.05
Aqueous	0.17	0.23	0.08	0.18	0.16	<0.005	<0.005	<0.005	<0.005	<0.005
Anterior uvea	0.25	0.88	0.46	0.43	0.50	<0.03	0.04	<0.02	<0.027	<0.058
Lens	0.05	<0.12	0.08	<0.06	<0.08	<0.01	<0.01	--	<0.01	--
Vitreous	0.02	0.06	0.02	0.02	0.03	<0.01	0.01	0.01	<0.005	0.01
Posterior uvea	0.22	2.5	0.27	2.1	1.27	<0.04	<0.033	<0.08	<0.03	<0.03
Sclera	2.3	6.7	2.6	7.5	4.8	<0.02	<0.03	<0.023	<0.02	<0.02

* Data after 24 hours.
† Data after 15 hours instead of 24 hours.

to try the penicillin ester in the same way. The results of the subconjunctival injections of 75,000 units of penethamate are so unanimously negative that the penicillin ester may be considered useless for this purpose. The excellent effect of subconjunctival injection of procaine penicillin is once more demonstrated.

In summary, these experiments demonstrate that there is not much difference between penicillin and the ester in passage from the blood to the aqueous. The vitreous, however, can be invaded by the ester only (Fig. 1). After subconjunctival injection, the effect of penicillin (or its procaine salt) is far superior to that of the ester. Injections with the latter have surprisingly little effect.

Comment

Penethamate is the hydroiodide of the diethylaminoethylester of penicillin G, the structural formula of which is given in Figure 2.

Parenteral administration results in an intramuscular or subcutaneous depot of the hydroiodide, which because of its relative insolubility provides a long-lasting supply of penicillin ester for the blood. Once in the blood, the ester is slowly split up by hydrol-

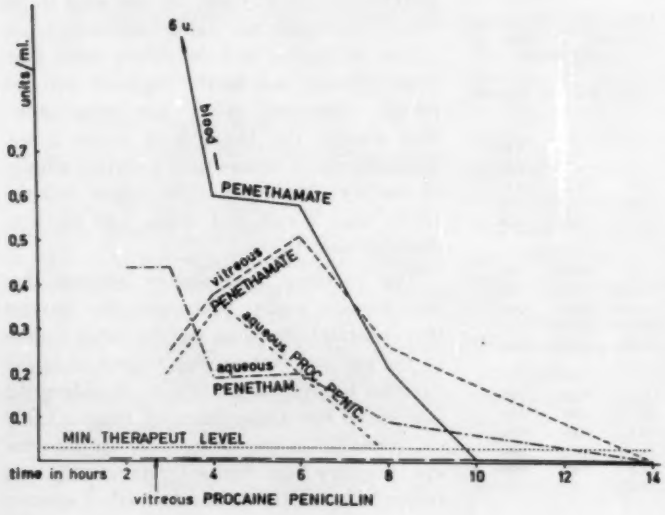

Fig. 1.—Penicillin levels in the aqueous humor and in the vitreous body after intramuscular injection of 100,000 units of procaine penicillin and 100,000 units of penethamate. The aqueous values are of the same order of magnitude. After administration of procaine penicillin, the penicillin concentration in the vitreous is negligible. Penethamate, on the other hand, produces penicillin levels in the vitreous of definite therapeutic activity. (Each value represents an average of at least four analyses.)

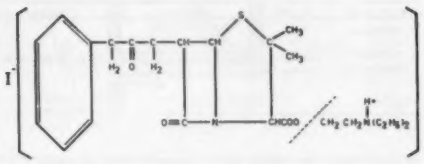

Fig. 2.—Structural formula of penethamate, the hydroiodide of diethylaminoethyl ester of penicillin G.

ysis into penicillin G and diethylaminoethanol. It has been estimated that after one hour only 15% of the penicillin ester is left (K. Hallas-Moller).[10] Unlike its component penicillin, the unhydrolysed ester has no antibiotic activity (K. Hallas-Moller).[10]

If a comparative study of the penetration of penethamate and penicillin is to be of any value, care should be taken to keep the concentration of the two compounds in the blood parallel. These comparable blood levels are easily obtained by treating the controls with procaine penicillin administered intramuscularly, which provides a flow of penicillin that lasts a long time. From the experiments it is evident that the concentrations in the blood after injections of penicillin and penethamate are so clearly comparable (Table 1) that a comparison of the penetration into the eye is justified. This leads to considerations of practical and theoretical importance.

Practical Consequences.—As is generally agreed, intraocular infections of the anterior segment of the eye are effectively dealt with by subconjunctival injections of penicillin or streptomycin or, if necessary, a combination of the two.

After perforation of the bulbus by either trauma or operation, the subconjunctival injection may be a hazardous manipulation. In such a case, the blood must be depended on to provide the eye with the necessary antibiotics, of which chloramphenicol was formerly the only suitable one.

These experiments make it evident that penethamate is a useful addition to the limited possibilities. Parenteral administration results in substantially high levels in all the tissues of the eye. From 500,000 units three times a day a blood level (1.25 units per gram) may be expected which is sufficient to provide even the central parts of the human eye with a penicillin concentration of therapeutic value.

Penethamate, containing iodine as well as penicillin, may produce allergic reactions in patients sensitive to these substances.[11] Care should be taken to avoid intravenous injection of penethamate, as this has been followed by convulsions (Engelbreth-Holm and Roholt).[12]

Theoretical Considerations.—Of theoretical interest is this question: "Does a vitreous barrier exist?"

Introducing his revolutionary theory about the formation of the aqueous in 1932, Duke-Elder in his textbook summarized the general opinion hitherto obtaining, in the following sentence: "In the physiological sense all the fluid inside the eye, with the exception of that contained within the blood vessels, should be considered as a unity—the fluid contained within the anterior and posterior chambers, that percolating the vitreous body as well as the tissue fluids of the eye."[13] Regardless of the problems of secretion, filtration, and thermodynamic equilibrium, the analysis of Table 1 demonstrates that no such unity exists. The penicillin concentration in the aqueous after systemic administration of procaine penicillin ranges from 0.24 to 0.42 units per gram, while the vitreous contains only traces. This constant difference suggests a barrier, at least between these media.

In 1948 Duke-Elder and Davson made the same observation after studying the penetration rate of sugars from the blood into the eye.[14] Using glucose, they found the concentrations in the aqueous invariably greater than those in the vitreous. Since, however, they were able to demonstrate a certain amount of consumption of glucose from the vitreous by the lens and by the retina which might be responsible for this discrepancy, this difference could not be regarded as proving the existence of a vitreous barrier. By using carbohydrates other than glucose, local consumption could be eliminated. Never-

theless, the vitreous did not contain any appreciable amount of these substances, whereas the aqueous contained a fair amount. This difference was a reason for assuming that the penetration rate into the vitreous was consistently smaller than that into the aqueous and that there must be a more selective barrier to diffusion into the vitreous body than that which separates the aqueous from the blood (Duke-Elder and Davson).[14]

According to Table 1, penicillin G acts in the same way as the sugars. It must still be established, however, that local destruction or consumption of penicillin is not the cause of the remarkable low levels in the vitreous. The estimates of the penicillin concentration are, after all, based on antibiotic activity, and this is known to disappear completely with alterations in the penicillin molecules. In this way penicillin G might possibly enter into the vitreous in reasonable quantity, despite a low reading of the biological tests.

The experiments with penethamate demonstrate the possibility of long-lasting antibacterial levels in the vitreous. As the ester has no biological activity of its own, these levels must be attributed to penicillin set free by local hydrolysis, which implies that penicillin is not inactivated in the vitreous. This fact is confirmed by the experiments of Ullberg, who was unable to detect any amount of radioactivity in the vitreous humor of rats after parenteral administration of labeled penicillin G. If, in the vitreous, the penicillin molecule was broken down into biologically inactive components, the radioactivity would still have been demonstrable.[15]

Thus, the striking difference in the concentration of penicillin in the aqueous and the vitreous after intramuscular injection of procaine penicillin does not result from the breaking down of penicillin into biologically inactive components but must be explained by the inability of free penicillin to pass into the vitreous. This is a strong argument in favor of the existence of a "vitreous barrier." This vitreous barrier is far from identical with the well-known blood-aqueous

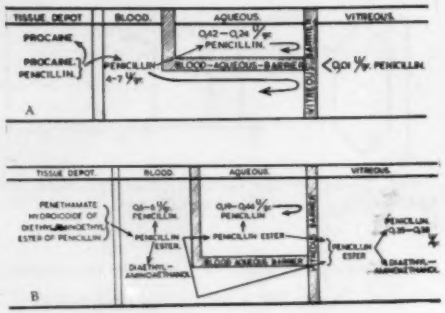

Fig. 3.—Diagrams illustrating the selective properties of the vitreous barrier. *A*, distribution from a procaine penicillin depot. *B*, distribution from a penethamate depot. The penicillin ester penetrates easily into the vitreous humor, whereas free penicillin is unable to do so.

barrier. It is definitely located between the aqueous and the vitreous humor and possibly extends around the entire surface of the latter.

The following facts suggest that the vitreous barrier does not merely act as a sieve but that it has selective properties. As stated before, procaine penicillin parenterally administered results in free penicillin G in the blood which penetrates to a certain extent into the aqueous but cannot pass the vitreous barrier (Fig. 3*A*). Penethamate administered parenterally provides the blood with the penicillin ester, which subsequently hydrolyzes into free penicillin G and diethylaminoethanol. In this way, the blood contains the ester and free penicillin simultaneously (Fig. 3*B*). Since only penethamate produces antibacterial activity in the vitreous (which must be attributed to free penicillin), and since free penicillin as such is unable to pass the vitreous barrier, it must be the ester which passes it. From Table 1 it is evident that the ester penetrates so easily that the antibacterial levels in the vitreous equal those in the aqueous and in the end even surpass them (Table 1, Penethamate 4 hrs. and 6 hrs.). This difference is the consequence of a small chemical addition to the penicillin molecule and demonstrates the qualitative selectivity of the vitreous barrier. Since the bigger molecules of the ester pass easily while the smaller ones of penicillin itself

are unable to do so, this qualitative selectivity of the barrier may not be attributed merely to "sieve-like properties" but must originate in a more complex mechanism, the nature of which will be discussed presently.

From the work of Davson, Duke-Elder, and other authors it is evident that carbohydrates, sulfonamides, and antibiotics penetrate more readily from the blood into the eye as the molecular weight is smaller, the rate of ionisation is lower, and the lipoid solubility is more pronounced.[14] Langham has demonstrated that chloramphenicol easily penetrates from the blood into the eye, having a lipoid solubility 10,000 times that of penicillin, streptomycin, chlortetracycline, and oxytetracycline.[16] Of the latter, chlortetracycline and oxytetracycline reach neither the aqueous nor the vitreous humor, while penicillin and streptomycin reach the aqueous only.[2-5,17]

Following Langham, an estimate was made of the lipoid solubility of penethamate under the conditions described in his paper (Table 5). Although the difference between chloramphenicol and penicillin is more spectacular, the fat-solubility of the penicillin ester is still 60 times that of penicillin, a difference which might be one of the factors responsible for the superior penetration of penethamate into the vitreous. This would imply that the vitreous barrier is less resistant to substances with fat-soluble properties.

Finally, the behavior of free penicillin and the penicillin ester suggests that the vitreous barrier is independent of the blood-aqueous barrier. The aqueous values in Table 1 are of more or less the same order of magnitude for the two substances. The vitreous concentrations, on the other hand, show a striking difference, the values of the ester amounting to 20-50 times those of free penicillin, which in fact scarcely penetrates at all. Unlike the blood-aqueous barrier, the vitreous barrier obviously rejects free penicillin and tolerates the ester.

Thus, proof is furnished (1) that the vitreous barrier exists, (2) that it has selective properties, and (3) that it acts independently of the blood-aqueous barrier. Once again it is evident that the vitreous body has a climate of its own, subject to the properties of its limiting border, the vitreous barrier. Attention is again drawn to the possibility that the intraocular pressure may show repercussions from the osmotic conditions of the vitreous body.

TABLE 5.—*Ether/Water Partition Coefficient*

	Ether/Water Partition Coefficient *	Authors
Penicillin	0.0004	Langham
Procaine penicillin	0.0003	Langham
Chloramphenicol	4.25	Langham
Penethamate	0.025	Bleeker and Maas
Chloramphenicol †	3.6	Bleeker and Maas

* In 0.01 phosphate buffer pH 7.4.

† To compare our results with those obtained by Langham's technique, the value of chloramphenicol was also estimated.

Summary

Experiments in rabbit eyes reveal that penicillin parenterally administered as procaine penicillin penetrates from the blood into the aqueous humor. The vitreous contains only traces. Penicillin parenterally administered as penethamate, a penicillin ester, reaches the aqueous in the same concentration, but penetrates readily into the vitreous.

Practical Result.—In infections of the inner eye, penethamate provides a useful addition to the limited therapeutic arsenal.

Theoretical Results.—The outcome of the experiments demonstrates that, in addition to the blood-aqueous barrier, there must be a vitreous barrier with selective properties and an independent function. The vitreous body must be considered as an individual unit with its own chemical and osmotic climate.

Mrs. E. van Maanen-Helmer, Mr. Lammens, and Mr. Gaemers gave assistance.

Muzenplein 1.

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The Elastic Properties of the Human Eye

FRANK J. MACRI, Ph.D.; THEODOR WANKO, M.D., and PATRICIA A. GRIMES, B.A., Bethesda, Md.

Introduction

The rigidity of the eye as defined by the equation of Friedenwald

$$K=\frac{\log P_2-\log P_1}{\Delta V}$$

has been shown to vary in the rabbit [1] and cat [2] with changes of the intraocular pressure (IOP). These observations are of interest because they might apply to the human eye and be relevant to the tonographic measurement of facility of outflow. In tonography, as presently practiced, it is presumed that the "rigidity" of the eye does not vary at different pressure levels, and calculations for facility of outflow are made on this basis. It thus becomes important to determine whether the human eye behaves as the eye of the cat and rabbit or whether it indeed has a constant coefficient of rigidity, as supposed by Friedenwald.[3]

Methods

Nine human eyes were examined in this study. Six of these eyes (Eyes 1 to 6) were received from the Buffalo Eye Bank, stored in refrigerated isotonic saline. Three eyes were obtained from the pathology department of the National Institutes of Health. Two of the latter eyes were examined in situ.

Refrigerated enucleated eyes were warmed in preheated isotonic saline to room temperature and then placed in cups and maintained with the cornea in an upward position, with the support of moistened pledgets of cotton. Two No. 27 stainless steel hypodermic needles were inserted into the anterior chamber at the limbus. One of these needles was connected, prior to insertion, to a 5 cm. length of No. 10 polyethylene tubing, which in turn was connected to a calibrated syringe microburet (Model SB2, Micrometric Instrument Company) of a construction similar to that used in this laboratory previously [2]; thus, known volumes of fluid could be introduced at will. In a similar manner, the second needle was attached to 5 cm. of tubing which was connected with a Statham transducer Model P23BB and an appropriate amplifier and recording system. The amplifier was adjusted to produce an excursion of 4 mm. for a change of pressure of 1 mm. Hg on the paper of the continuously recording instrument. The two systems were meticulously checked for the presence of air bubbles before and after the insertion of the needles. The procedure for infusion and pressure recording was the same for both enucleated eyes and eyes in situ.

Fixed volumes (5 and 10 cu. mm.) of saline were infused until pressures of 80 to 100 mm. Hg were attained. With the exception of Eye 5, duplicate determinations were made on each eye. The incremental pressure values were extrapolated to zero time. The necessity for this procedure has been previously explained.[2]

Results

The pressure readings obtained by the infusion of fixed volumes of saline into the anterior chamber (in one case, Eye 6, by vitreous infusion) were plotted directly as pressure increment versus volume increment for each eye studied. Figure 1 shows

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

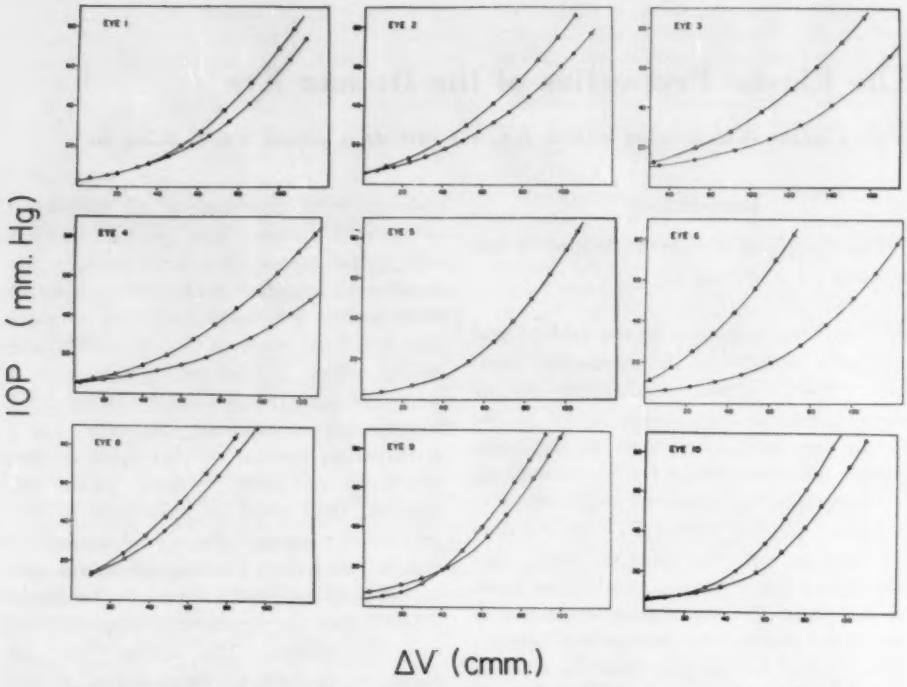

Fig. 1.—Pressure-volume relationship of human eyes found by two consecutive determinations. Plots of pressure increments induced by known volumes of infusate in duplicate trials produce curves which appear to be dissimilar. Dots identify the curves obtained in the first determination, and triangles, the second. The volume scale in this Figure and in Figure 2 is not intended to imply a known initial volume of the eye, but only to indicate relative volume changes.

the curves of the volume-pressure relationship of duplicate determinations for each eye, with the exception of Eye 5, in which only one determination was made. It is obvious that the two curves derived from individual eyes in consecutive determinations appear to have different slopes. However, if the two curves are superimposed as in Figure 2, it can be seen that the curves are identical but that corresponding absolute values of pressure differ by a constant amount, usually not more than 5 mm. Hg. The differences in the slopes between the curves at the first determinations (Fig. 1) seem to depend on the time intervals which had elapsed after death. The eyes were therefore grouped according to this time factor. The slopes $\frac{(P_2-P_1)}{\Delta V}$ at the various pressure levels of those examined at 30 minutes (Eyes 9 and 10), 12 hours (Eyes 1, 2, 6, and 8), 24 hours (Eyes 3 and 4) and 4 days (Eye 2) after death were plotted against the mean intraocular pressure $\frac{(P_2-P_1)}{2}$ (Fig. 3).

The rigidities of the eyes calculated by the equation of Friedenwald [3]

$$K \text{ (rigidity)} = \frac{\log P_2 - \log P_1}{\Delta V}$$

where

P_2=final pressure

P_1=initial pressure

ΔV=volume change

are plotted in Figure 4 as a function of IOP. As the IOP increases, it may be seen that the rigidity of some eyes increases up to a critical point and then begins to decrease, while in other eyes only a decrease of rigidity can be observed.

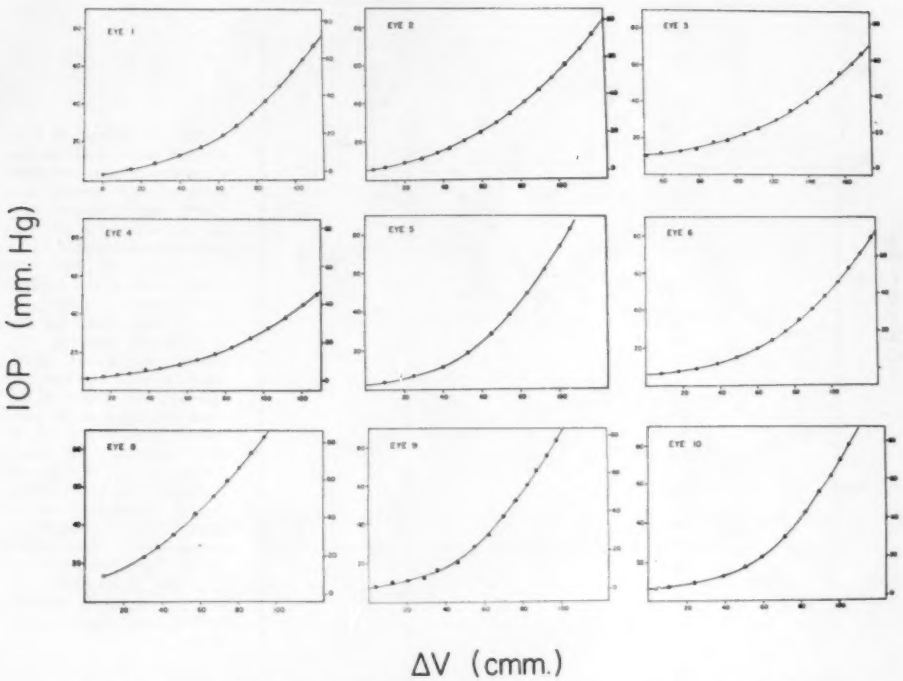

Fig. 2.—Superposition of the duplicate pressure-volume curves of Figure 1. The pressure scales on the left and on the right of each plate represent the absolute pressures of the first (dots) and second (triangles) trials, respectively. It may be seen from this Figure that the two curves can be superimposed with a very good fit. The absolute pressure difference of the superimposed curves does not exceed 5 mm. Hg and represents, in pressure equivalents, the amount of irreversible stretch induced by the first pressure-volume determination.

Comment

Comparison of Duplicate $\Delta P/\Delta V$ *Determinations in Individual Eyes.*—Many elastic substances subjected to a stress do not necessarily return to the dimensions existing prior to the stretch when the stress is removed. This phenomenon was noted, by Ridley, to occur in the excised human eye.[4] The quantity of dimensional change is known as "set." Each subsequent determination of stretch has to consider the "set," or dimensional change, when determining the starting point for that determination. Thus, two consecutive determinations of stretch for an elastic substance should be identical after correction for "set."[5]

Plots of experimental results as ΔP vs. ΔV (Fig. 1) indicate that the duplicate determinations of individual eyes seem to deviate from each other in slope of ascent. However, the curves plotted for each eye can be superimposed, as seen in Figure 2, and demonstrate a very close fit.

By the above criteria, it appears that the eyes undergo a certain amount of "set" after the first series of determinations, which cannot be defined in terms of volume change. The "set" can, however, be expressed as the difference of the absolute pressures at any point on the superimposed curves (Fig. 2). If it is presumed that the dead eye has a certain amount of "set," evidenced after a first series of determinations, the data of the second trials cannot be used, uncorrected, for grouping in order to arrive at mean values for duplicate trials.

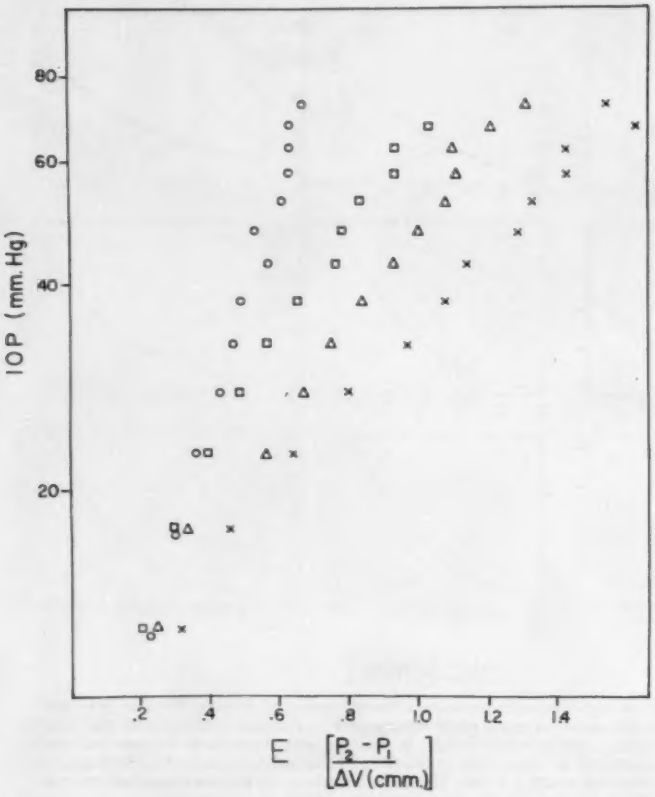

Fig. 3.—Effect of time elapsed after death on the pressure-volume relationship of the human eye. Coefficient of stretch (E) as expressed in the abcissa was calculated from the slopes of the first trials made for the pressure-volume functions of these eyes (Fig. 1) and is plotted against the mean intraocular pressure. It may be seen that the $\Delta P/\Delta V$ slopes of the eyes examined at 30 minutes (Eyes 9 and 10, in situ, crosses), 12 hours (Eyes 1, 2, 6, and 8, triangles), 24 hours (Eyes 3 and 4, squares), and 4 days (Eyes 2, circles) increase with time after death. This demonstrates that the distensibility of the eye increases relative to the time elapsed after death.

The second trials, thus, in this report serve only to indicate the reliability of the results obtained in the first determinations.

"Set" when expressed in terms of pressure was determined in all eyes to be approximately 5 mm. Hg, irrespective of the time intervals, in these experiments, elapsing between death or enucleation and the experimental determinations.

Comparison of $\Delta P/\Delta V$ *Relationship Between Individual Eyes.*—All of the eyes examined in this study had similar slopes for the ΔP vs. ΔV relationships; i. e., fixed volumes of infusate caused greater increases of the intraocular pressure, as the level of the intraocular pressure rose. These observations are in general agreement with those previously reported by Ridley[4] and Clark[6] for the human eye. It can be noted, in Figure 2, that, although the slopes (ΔP vs. ΔV) are similar, they are not sufficiently close to arrive at a mean value for all eyes without a very large standard deviation. It seemed probable that the variations in the slopes might have been due to differences in extent of postmortem changes. This is substantiated by Figure 3, in which the data expressed as $\Delta P/\Delta V$ versus intraocular pressure are pooled into four groups, according to the time elapsed (30 minutes, 12 hours, 24 hours, 4 days) between death and the experimental determinations. The rate of ascent of the curves declined directly in relation to the time interval between death and the experimental procedure. The patients' diseases did not appear to influence these patterns. With the exception of Eyes 9 and 10, the eyes studied were from persons of the same age group (Table), and so no correlation between donor's age and slope is

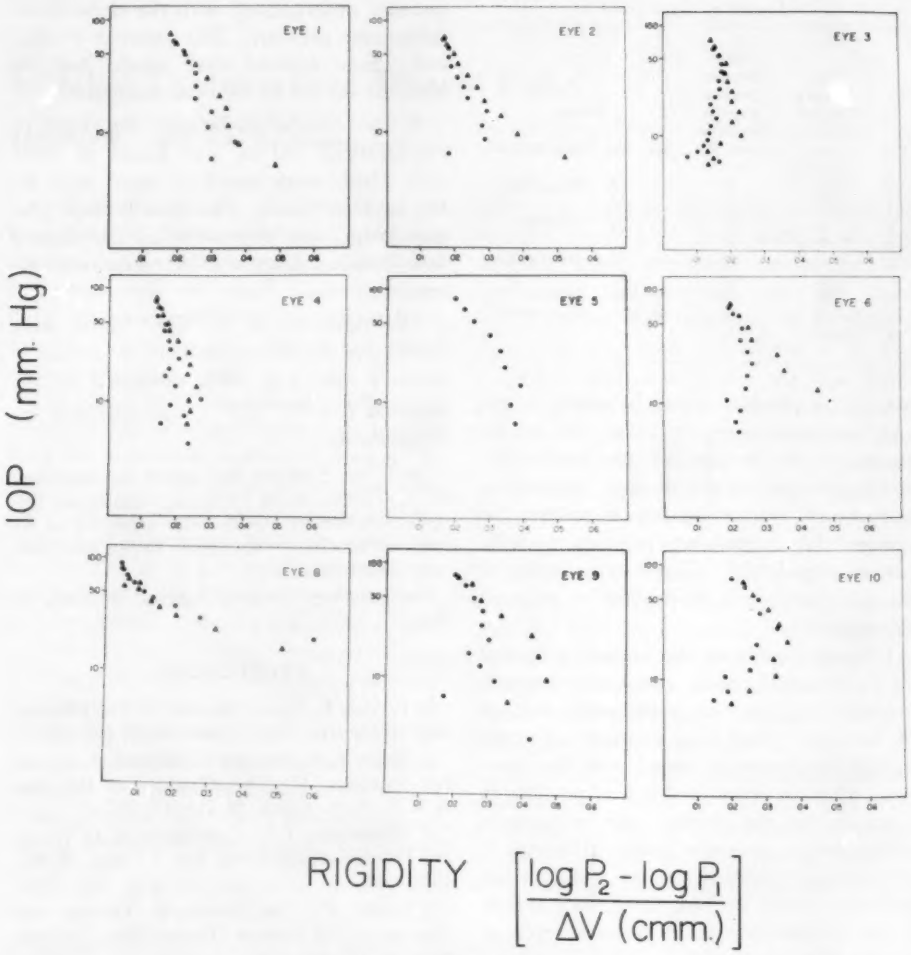

Fig. 4.—Rigidity calculated by $K=\frac{\log P_2-\log P_1}{\Delta V}$ as a function of intraocular pressure. Rigidities of the duplicate trials as seen in Figure 1 were calculated by the formula proposed by Friedenwald and plotted versus the mean intraocular pressure. Dots represent the rigidities obtained in the first determinations, and the triangles, those obtained in the second. The erratic nature of the curves and their dissimilarity from each other is apparent.

apparent to explain this difference. That the variations in responses were most likely due to postmortem changes is supported by the changes noted in Eye 2 when tested at 12 hours and 4 days after the patient's death. A marked decrease in the rate of ascent of $\Delta P/\Delta V$ was found at 4 days when compared with that found at the 12-hour interval. This correlates well with the findings in the other eyes.

In order that confusion with the term "rigidity" as defined by Friedenwald may be avoided, it is suggested that E be called "coefficient of stretch." In this text, then, E is called "coefficient of stretch" and is defined as $E=\frac{\Delta P}{\Delta V}$. The elasticity patterns reported here apply only to enucleated eyes or eyes tested in situ, 30 minutes post mortem, at which time no signs of rigor mortis were present. It is essential in order to

Source of Eyes Used

Eye	Time Between Death & Enucleation, Hr.	Time Between Death & Rigidity Determination, Hr.	Patient		
			Age	Sex	Cause of Death
1	½	12	74	M	Heart attack
2	½	12			
3	2	24	92	M	Unknown
4	2	24			
5	2	12	50	M	Cancer of lung
6	2	12			
8	11	12	60	F	Cancer
9	In situ	½	23	F	Brain tumor
10	In situ	½			

obtain comparable values between in situ and enucleated eyes that there be no increase in the tension of the extraocular striate muscles of the in situ preparation. Increase of extraocular muscle tension can change the intraocular pressure-elasticity pattern considerably. The results relating to the aforementioned effects will be reported subsequently.

Plotting rigidity by the formula proposed by Friedenwald versus intraocular pressure produced no constant relationship for all of the eyes (Fig. 4). In some eyes the rigidity continuously varied with the pressure, while in other eyes it was possible to conclude that the rigidity may be constant within certain pressure limits. Although E certainly is variable in any one eye over the pressure ranges studied, there does appear to be a constancy of E between eyes at similar pressure levels.

Summary and Conclusions

The elasticity of the dead human eye calculated by the use of the formula E (coefficient of stretch) $=\Delta P/\Delta V$ was found to increase progressively with the elevation of intraocular pressure. The patterns of elasticity thus obtained were similar but not identical for all of the eyes examined.

A close parallelism between the slopes of the elasticity curves was found in those eyes which were tested at equal time intervals after death. The eyes became progressively more distensible as the elapsed time between death and determinations increased.

The rigidities of the eyes tested were found not to be a constant at pressures above 5 mm. Hg, when calculated by the equation $K=\frac{\log P_2-\log P_1}{\Delta V}$, as supposed by Friedenwald.

Dr. L. von Sallmann gave advice and assistance. Dr. L. Thomas, of the Pathology Department, National Institutes of Health, made a number of the eyes available to us. Mr. Joseph Brown gave technical assistance.

Ophthalmology Branch, National Institutes of Health.

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Isolated Cyclovertical Muscle Palsy

MARSHALL M. PARKS, M.D., Washington, D. C.

Each of the muscles that move the eye in a vertical plane about the transverse equatorial axis also renders a torsional movement about the anterior-posterior axis (Fig. 1). An abnormality of one of these muscles is manifest by a combined cyclovertical phoria or tropia.

The nature of eye movement produced by a cyclovertical muscle contraction depends upon the horizontal position of the eye. In the position of abduction, the vertical recti move the eye in the vertical plane and the obliques, in a torsional plane. In adduction, the vertical recti act torsionally and the obliques, vertically. Both the vertical recti and the obliques deliver a combined vertical and torsional action in the primary position; however, the action of vertical recti is somewhat more vertical whereas the action of the obliques is more torsional. Weakness of a single cyclovertical muscle is characterized therefore by vertical and torsional deviation in the primary position. The torsional deviation increases on lateral gaze to one side, while the vertical deviation increases on opposite lateral gaze. For example, a right superior rectus weakness results in left hypertropia that increases on right gaze and extorsion that increases on left gaze, since it is an elevator and intorter (Fig. 1).

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Ocular torticollis is one of the well-known telltale signs of cyclovertical muscle paralysis. However, the head-tilted position is not invariably present for the purpose of making binocular vision possible, as Bielschowsky [1] claimed. Ocular torticollis often accompanies cyclovertical muscle palsy in the absence of fusion ability. It is interesting that Manzitti and Ciancia [2] discovered the head-tilt to vanish in 10 cases of superior oblique paralysis, regardless of whether fusion was present, when the involved eye was occluded. Occlusion of the sound eye had no such effect.

One of many outstanding contributions Bielschowsky [1] made to ophthalmology was his insistence that attention be paid to the torsional element in cyclovertical strabismus. But he was unable to reconcile a dif-

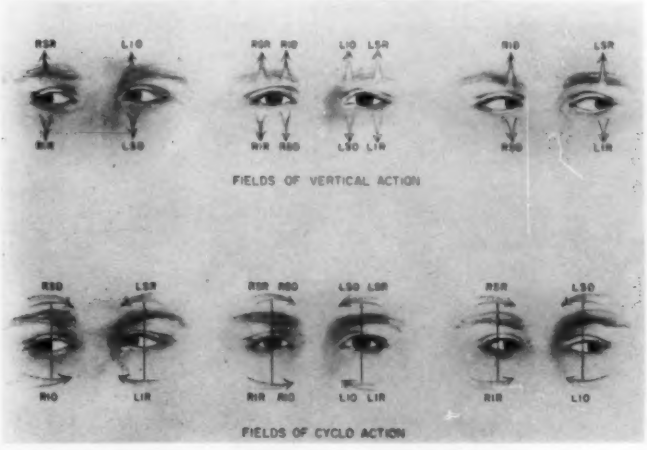

Fig. 1.—Vertical fields of action and cyclo fields of action of cyclovertical muscles.

ference, which even he recognized, between his extraordinary insight of cyclovertical muscle physiology and his clinical impression that all ocular torticollis was associated with an oblique muscle paralysis. Bielschowsky [1] wrote, "I have not yet been able to find out why tilting is of no use in palsies of the vertical recti, although these muscles help to bring about rotation of these eyes around the visual axis necessitated by tilting the head toward the opposite side. According to my experience, paresis of the superior or inferior oblique is in all cases at the bottom of ocular torticollis provided that only by this posture can binocular single vision be obtained." This clinical impression of Bielschowsky has not withstood the test of time, and more modern textbooks, such as Chavasse [3] and Duke-Elder,[4] illustrate head-tilting accompanying vertical rectus palsy.

Torticollis should arouse all physicians to investigate for cyclovertical strabismus. But torticollis secondary to cyclovertical strabismus does not automatically indicate the presence of binocular vision, nor does it mean that the palsied muscle is an oblique. Most important, from a diagnostic point of view, is Krewson's [5] observation that torticollis is not of a stereotyped pattern for each weak cyclovertical muscle. Consequently, in order correctly to diagnose which cyclovertical muscle is weak, more than a simple observation of torticollis is necessary.

The diagnosis ultimately must depend upon deductions made from vertical imbalances observed in various gaze and head positions. The vertical imbalance is measured directly by such methods as the Krimsky corneal reflex and prism alternate cover or indirectly by diplopia field studies. Reliable diplopia fields are impossible to obtain in children below the age of 4.

Diagnosis

I wish to describe a system of investigation and reasoning, which, if followed, will quickly and accurately provide the diagnosis of the weak muscle causing the vertical imbalance. The system is comprised of three diagnostic steps. Each step reduces by one-half the number of muscles that could possibly cause the imbalance. The first step immediately cuts the diagnostic possibility from eight cyclovertical muscles to four; the second step reduces it to two muscles, and the third step indicates which one of the remaining two muscles is weak.

The first diagnostic step is simply to determine whether there is right or left hypertropia in the primary position. Figure 2 illustrates that a right hypertropia (RHT) can be observed from corneal light reflections or from prism and alternate cover measurements or can be presumed from diplopia studies. The particular variety of diplopia study illustrated is the Strabismom-

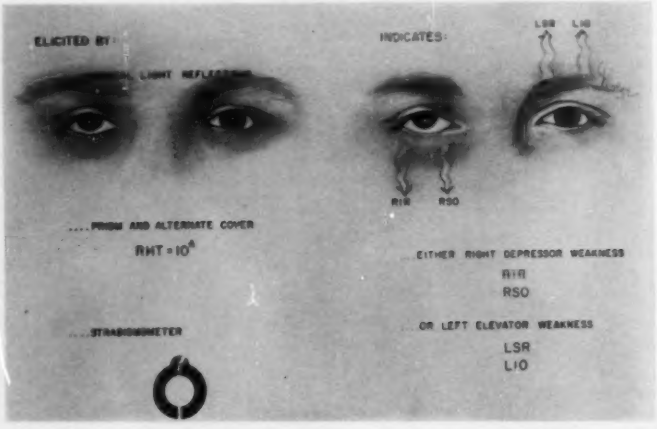

Fig. 2.—First diagnostic step. RHT in the primary position indicates either right depressor or left elevator weakness.

eter.* Studying cyclo errors is not a part of the diagnostic system I am presenting, but since the Strabismometer affords a simultaneous study of both vertical and cyclo errors, the realistic findings of both are illustrated. In this case, the red lens is before the fixating left eye. The RHT is evident from the green disc being misplaced above the center of the red ring, and incyclotropia is apparent by virtue of the superior pole of the cyclo check line tilting inward. For the sake of simplicity on this and subsequent composite sketches, the cyclo check line of the green target is tilted as though viewed by the examiner facing the patient, but on the opposite side of a semitransparent screen from the patient. Interesting as this cyclo element may be, its analysis is not vital to the diagnostic steps being presented. The important fact in Step 1 is that the RHT is present in the primary position. This narrows the diagnostic possibilities as to which cyclovertical muscle is paretic from eight to four. RHT indicates that either a depressor in the right eye or an elevator in the left eye is weak. The right depressors are the superior oblique and inferior rectus, and the left elevators are the superior rectus and inferior oblique.

The second diagnostic step is a comparison between the quantity of vertical deviation in right and left gaze. Figure 3 indicates that the RHT increases on right gaze and diminishes on left gaze. Therefore, the right inferior rectus and left inferior oblique are kept under suspicion, since their fields of vertical action are in right gaze. Moreover, both of these muscles are extorters. Consequently, a weakness of either causes incyclotropia which increases on left gaze. But again, the pertinent fact of Step 2 is that the RHT increased in right gaze. This narrows the diagnostic possibilities from four to two muscles.

Two things should be emphasized at this point: (1) the two muscles under suspicion are always in different eyes and (2) both are always either inferior or superior muscles. The suspected culprits from Step 2 will always be the inferior rectus of one eye and the inferior oblique of the other, or the superior rectus of one and the superior oblique of the fellow eye. Never are the superior muscle of one and the inferior of the other eye implicated. Please

* The Strabismometer (House of Vision, Chicago) is a modification of the Lancaster red-green projectors. Through red-green spectacles the patient views the red doughnut with one eye and the green disc with the other. Each is projected by individual projectors onto a screen. A meridian of each, the red doughnut and green disc, is blocked out, which affords a means of detecting cyclo errors. The patient holds the green projector and attempts to place the green disc in the center of the red ring, thus making the vertical line separating the disc and ring appear continuous.

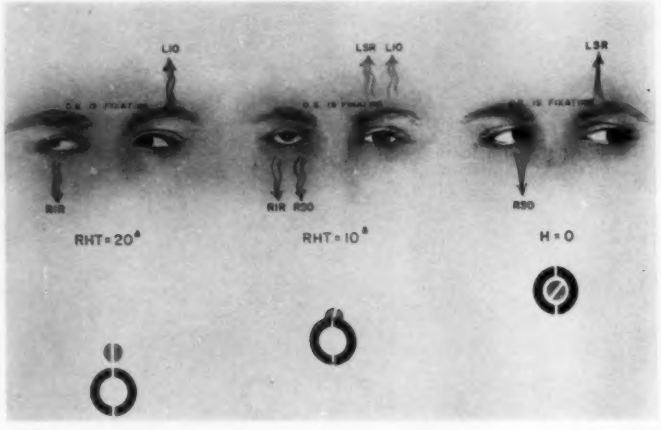

Fig. 3. — Second diagnostic step. An RHT that increases in right gaze indicates either RIR or LIO weakness.

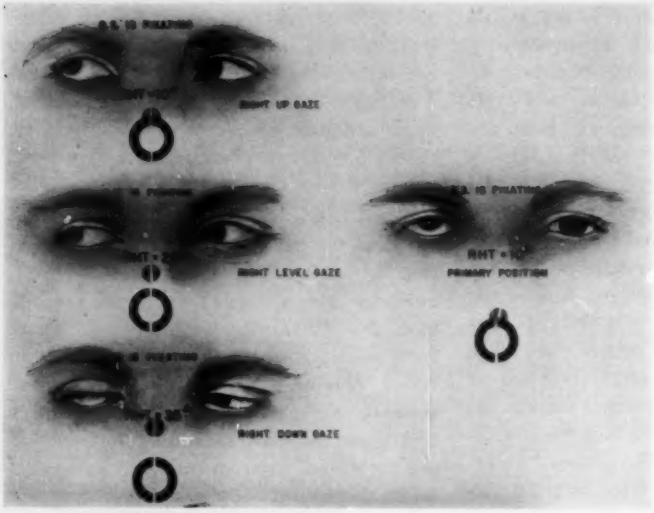

Fig. 4.—Illustration of right inferior rectus palsy of recent onset.

recall that inferior muscles, i. e., inferior rectus and inferior oblique, are extorters; superior muscles, i. e., superior oblique and superior rectus, are intorters. Consequently, the two accused muscles revealed by Step 2 are either both extorters or both intorters. This realization is helpful in the execution of the next diagnostic step, which indicates the weak muscle of the two under suspicion.

It follows, as Figure 4 depicts, that the third diagnostic step should be a comparison of the vertical deviation in the cardinal positions of up and down gaze while the eyes are directed to the side of greatest vertical misalignment. A right hypertropia greatest on looking right would implicate either the right inferior rectus or the left inferior oblique. Theoretically, right inferior rectus weakness causes the right hypertropia to increase on down and right gaze but to decrease on up and right gaze. The reverse should occur in left inferior oblique weakness. These findings are ordinarily found in freshly palsied muscles.

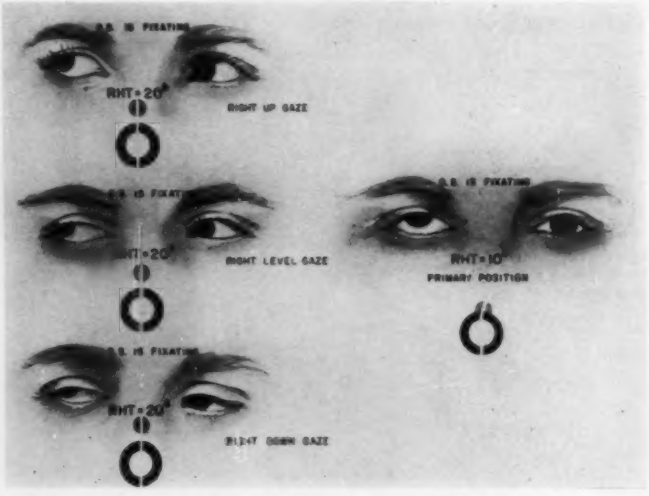

Fig. 5.—Illustration of congenital left inferior oblique palsy.

But, in palsies of long standing, this nebulous thing referred to as hypertrophy, shortening, or contracture of the direct antagonist may erase the expected noncomitant RHT in right gaze, replacing it with comitant RHT. Figure 5 is an example of the findings associated with long-standing left inferior oblique palsy. Reliance upon cardinal field studies may lead to the wrong diagnosis, especially if, as illustrated, the paretic muscle is on the fixating eye. During fixation with the left eye in down and right gaze, less opposition from the weak left inferior oblique allows the hypertrophied left superior oblique to depress the left eye further than the normal right inferior rectus depresses the right eye. So, in gross version studies the right inferior rectus appears palsied, but actually it is the normal contralateral antagonist to the palsied left inferior oblique. Bielschowsky [1] first directed attention to how easy it is to commit this error and described his head-tilt test for avoiding it. In fact, this diagnostic error has been so frequently committed that Chavasse [3] gave it the imposing title of inhibitional palsy of the contralateral antagonist. Adler [6,7] has more recently emphasized this same fact and pointed out the importance of the head-tilt test to insure against diagnosing the wrong muscle.

Therefore, the Bielschowsky head-tile test is the third diagnostic step. The weak muscle of the two intorters or extorters brought under suspicion by Step 2 is differentiated by determining to which side the head must be tilted to cause maximal hypertropia. Before the pathological physiology revealed by the Bielschowsky head-tilt test can be grasped, the normal physiology of the extraocular muscle response to head-tilting must be understood. Figure 6 shows that with the head tilted right the right intorters and left extorters contract, and with left tilt it is the right extorters and left intorters which contract. But since the eyes remain in the primary position with reference to the skull, despite the change of the head position in the field of gravity, the contracting cyclovertical muscles render a combined torsional and vertical action. The two intorters or the two extorters of each eye that contract in response to head-tilt have opposite vertical actions; one is an elevator and the other, a depressor. Normally, the opposite vertical actions cancel each other, while their identical torsional actions are additive. Therefore, the eye remains on the same level in the vertical plane but cycloverts accordingly.

Figure 7 illustrates the Bielschowsky head-tilt findings in (*a*) a weak intorter and (*b*) a weak extorter. A palsied right

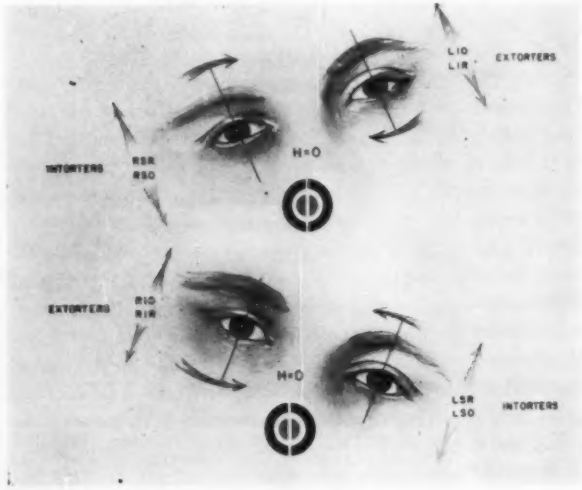

Fig. 6. — Bielschowsky head-tilt in the presence of normal cyclovertical muscles.

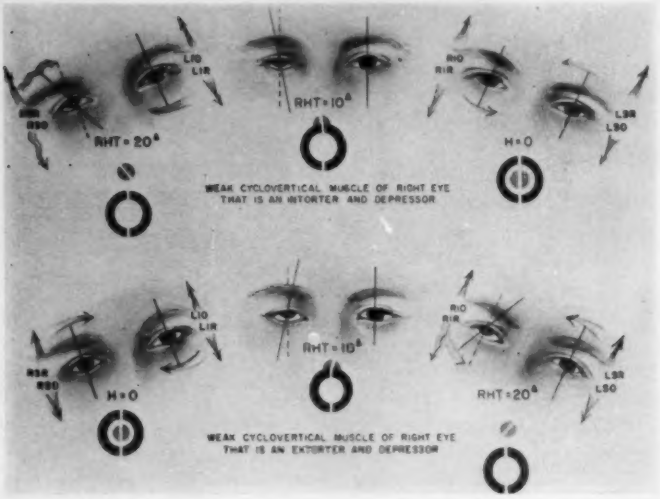

Fig. 7. — Bielschowsky head-tilt in the presence of a single weak cyclovertical muscle.

intorter is stimulated upon right head-tilt, and its deficient depressor action is unable to neutralize the elevator action of its normal fellow intorter. This causes an increase in the right hypertropia when the head is tilted right and a decrease upon left head-tilt. A palsied right extorter is stimulated on left-head tilt, and its weak depressor action is unable to offset the elevator action of its normal fellow extorter. Consequently, there is an increase in RHT on left head-tilt and a decrease on right tilt.

Since Step 2 has already delineated the suspected intorter in each eye, or the suspected extorter in each eye, the examiner realizes, prior to doing the head-tilt test, which eye is being tested upon tilting the head first right and then left. If the differential is between weak intorters, the muscle on the eye ipsilateral to the side to which the head tilts is tested. The eye opposite to the side to which the head tilts is tested if the weak muscle is an extorter. Therefore, the third diagonstic step, which is the Bielschowsky head-tilt test, differentiates which one of the muscles brought under suspicion by Step 2 is palsied, by showing to which side the head must be tilted to increase the hypertropia.

Figure 8 reviews the three diagnostic steps. First, a right hypertropia is apparent in the primary position. Second, it is greatest on right gaze. This implicates as being weak one of the following two extorters: (1) the left inferior oblique or (2) the right inferior rectus. With the knowledge that on right head-tilt the left inferior oblique is stimulated and on left tilt the right inferior rectus contracts, an increase of right hypertropia on right head-tilt establishes the diagnosis of left inferior oblique weakness. An increase of right hypertropia

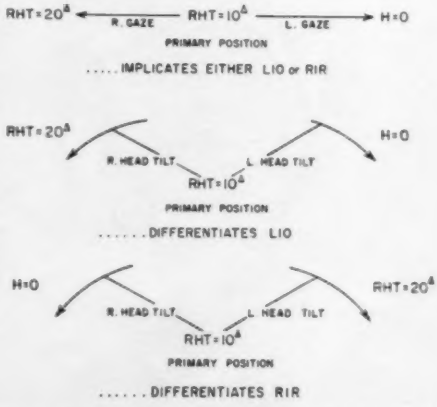

Fig. 8.—RHT that increases in right gaze is due to either right or left weak extorter. The Bielschowsky head-tilt test differentiates which one is weak.

on left head-tilt differentiates the right inferior rectus.

The foregoing is not entirely in keeping with Bielschowsky's [1] interpretation of head-tilt test findings. He attributed an increase in the vertical deviation on head tilting only to oblique muscle weakness, which, of course, parallels his concept on ocular torticollis. Just as his impression that oblique muscle weakness is exclusively at the bottom of ocular torticollis is no longer tenable, his assertion that a positive head-tilt test is caused exclusively by the oblique muscles is incorrect.

Etiology, Clinical Course, and General Management

The etiology, clinical course, and general management of strabismus caused by an isolated weak cyclovertical muscle are more easily presented by distinguishing two groups, congenital and acquired.

Congenital.—The motor nerve, cyclovertical muscle, or its attachments did not develop properly, and normal movement of the globe in the field of action of the involved muscle is precluded. It attracts clinical attention by 6 months of age because of either an obvious vertical strabismus or torticollis or both. Cyclovertical muscle surgery is indicated as soon as possible, even by the age of one year if the surgeon is confident about his clinical findings. Early surgery offers the only rational means of preventing the permanent musculoskeletal changes of torticollis, facial asymmetry, and scoliosis. Furthermore, the chance of developing or maintaining binocular vision is enhanced by surgically decreasing the obstacles to fusion at a tender age.

Acquired.—Involvement of the third nerve complex usually affects multiple extra and intraocular muscles. This makes single cyclovertical muscle weakness resulting from third nerve lesions a most remote possibility. Fourth nerve lesions are clinically manifest exclusively by superior oblique weakness. However, associated third or sixth nerve involvement may complicate the clinical picture. Some of the specific causes of fourth nerve paralysis are diabetes, herpes zoster, polyneuritis, meningitis, and hemorrhage in the roof of the midbrain resulting from arteriosclerosis.[8] Also, the superior oblique may be mechanically weakened as a result of injury being inflicted or surgery being performed in the neighborhood of the trochlea. Maxillary fracture and involvement of the orbital floor may weaken the inferior oblique. In fact, any cyclovertical muscle is capable of being weakened by trauma or surgery.

Diplopia is the chief symptom of acquired cyclovertical strabismus. The patient may be happier ridding himself of the diplopia by compensatory head posture, or he may prefer occlusion. Treatment during the first six months is usually waiting to determine the degree of spontaneous recovery unless surgical repair of a displaced trochlea or fractured orbital floor is obviously needed. Specific surgical correction of the acquired strabismus should not be delayed after six months from onset. It should be stressed that only one muscle at a time should be operated on and the degree of improvement studied over a three-month period prior to deciding whether further surgery is indicated. Overcorrection is easy to obtain.

Specific Surgical Management.—The problem of which muscle to operate on and how much should be done applies equally to the congenital and the acquired type. The surgeon's objective is to simultaneously improve the cyclo and vertical deviation. This can only be accomplished by adhering to the principle of confining the surgery to muscles whose cyclo and vertical field of actions coincide with the patient's field of maximal cyclo and vertical deviations. Consequently, more must be known about the strabismus than simply the vertical deviation measurement in the primary position. An absolute minimum includes knowledge as to the lateral gaze direction in which the vertical strabismus is greatest. Fortunately, this minimum knowledge about the direction in which the vertical deviation is maximal

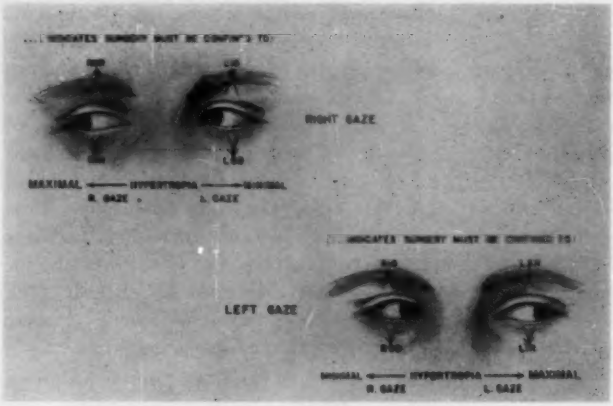

Fig. 9. — Hypertropia greatest in right gaze limits surgery to right vertical recti and left obliques. If greatest in left gaze, the surgery must be confined to right obliques and left vertical recti.

automatically assures not only the correct vertical surgery but also the correct torsional surgery. Figure 1 demonstrates that the vertical and cyclo fields of action for the same muscles are in opposite gaze directions from the primary position. For instance, the right superior rectus vertical action is in right gaze and its intortion action is in left gaze. Therefore, by operating on a muscle whose maximal vertical action coincides with the lateral gaze position in which the vertical strabismus is greatest, not only will the vertical deviation be correctly attacked but, automatically, so will the cyclo deviation. In other words, the surgeon cannot miss doing the proper cyclo surgery if the correct vertical surgery is done and vice versa.

Figure 9 shows the muscles that move the eyes vertically in right and left gaze. If the hypertropia is greatest in right gaze, the surgery must be confined to the right vertical recti and left obliques. A hypertropia maximal on looking left limits the surgery to only the left vertical recti and right obliques. But the important issue is which one of these four muscles should be operated on first in order to ensure the best chance that only one operation will give a satisfactory result. Before this decision can be made the two following matters must be resolved: 1. There must be a specific diagnosis of the palsied muscle. 2. The surgeon must have established a policy of whether he should first resect the paretic muscle, recess its ipsilateral antagonist, recess its yoke, or resect its contralateral antagonist.

Dunnington [9] stated in 1948 that his operative aim is to resect the affected muscle rather than recess the normal one. As an initial procedure, I have not found that it yields as high a degree of success as recessing the yoke. Since no amount of surgery will make the paretic muscle normal, resecting it can only mechanically improve the cyclovertical deviation in the primary position. But as the eyes move into the vertical field of action of the resected palsied muscle, the yoke still more effectively moves the opposite eye, which causes an increasing hypertropia, regardless of which eye is fixating. In recessing the yoke of the palsied muscle, improvement of the vertical imbalance is afforded in (1) the primary position and (2) the field of action of the palsied muscle. In other words, the best chance of balancing imbalanced yokes is to recess the normal one, and, with one very outstanding exception, this is the initial procedure I advise.

The exception I refer to is contracture of the ipsilateral antagonist, which, if this condition is present, should be recessed. A hypertrophied contractured direct antagonist overpowers the weak contraction of the paretic muscle, preventing what limited motility and positioning of the eye the paretic

muscle is capable of providing. Therefore, the ability of the paretic muscle cannot be assessed in the presence of such an antagonist. Moreover, the favorable operative results produced either by resecting the paretic muscle or by recessing its yoke are to a large degree negated.

Difficulty may arise over spelling out what is and what is not contracture, since it is often relative rather than absolute. In such a case, there is no substitute for clinical judgment. However, three separate clinical criteria suggest that the direct antagonist has undergone contracture: 1. As illustrated in Figure 5, the vertical deviation has become comitant for all three cardinal positions when the patient looks to the side of greatest hypertropia. 2. Secondary deviation no longer exceeds primary deviation. 3. The traction test under anesthesia may be positive for resistance offered in passive movement of the eye into the field of action of the palsied muscle.

Therefore, if contracture of the ipsilateral antagonist is apparent, this muscle should be recessed first. If it is not apparent, the yoke should be recessed. If a second procedure is indicated after initial recession of the contractured antagonist, the yoke should be recessed next. In the absence of antagonist contracture, the first procedure having been recession of the yoke, the safest second operation would be to resect the weak muscle.

Summary

An isolated cyclovertical muscle palsy can be quickly and accurately diagnosed by investigating whether the hypertropia is greatest in right or left gaze and right or left head-tilt.

If the antagonist of the palsied muscle is contractured, it should be the first muscle operated on; otherwise a recession of the normal yoke of the palsied muscle is advised.

2129 Bancroft Place, N. W.

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Primary Familial Amyloidosis

HERBERT E. KAUFMAN, M.D., Bethesda, Md.

Primary familial amyloidosis is a rare systemic disease of protean manifestations.[1-3] Ocular symptoms of amyloidosis result from (1) neuropathy secondary to deposition of the abnormal protein in the nerves, (2) vascular fragility and obstruction from amyloid deposition in the vessel wall, (3) functional impairment and structural distortion consequent to the mass effect of amyloid tumors, and (4) opacification of the vitreous.[4-23]

In Case 1 ocular symptoms are the earliest manifestation of the systemic disease. It is the first instance in which the vitreous opacities, seen to occur with the disease, are shown to be comprised of amyloid, and illustrates that these characteristic opacities may appear cellular as well as membranous and veil-like. Glaucoma is now documented in amyloidosis, though, in other cases, eye pain and blindness have occurred.[50-60]

CASE 1.—A 25-year-old single male stable groom, first noted dark spots, small flashing lights, cobweb-appearing opacities, and decreasing vision in the right eye in February 1954, but had no pain or photophobia at this time. The patient was hospitalized with a presumptive diagnosis of granulomatous uveitis and was treated first with penicillin and then with streptomycin and cortisone. Etiological work-up, including blood tests, tuberculin tests, and x-rays of the chest, hands, and feet, was negative. Three small cysts on the head were excised, but pathologic examination revealed only sebaceous cysts.

In March, 1954, similar symptoms developed in the left eye, and in January, 1955, the patient was seen at the National Institutes of Health.

Family history will be discussed below.

Past History.—A brief bout of dysuria, hematuria and back pain occurred in September, 1952. Despite a 10 lb. weight loss during the year before admission, the patient's appetite, energy, and general physical condition appeared excellent.

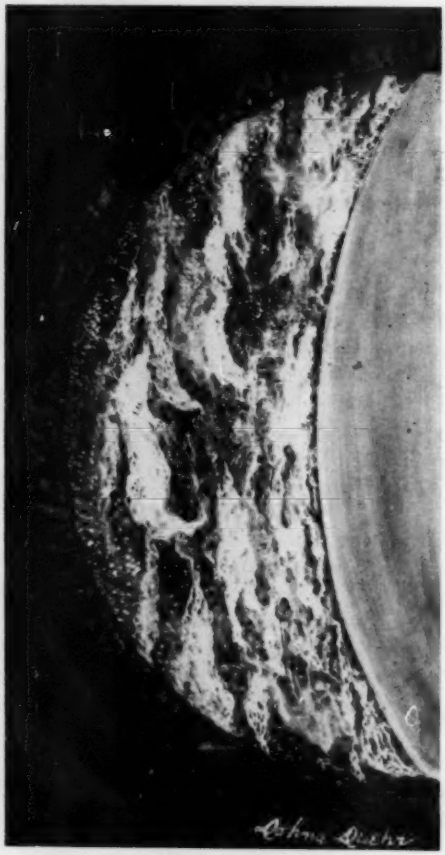

Fig. 1.—Drawing of the slit-lamp appearance of the vitreous of the left eye.

Submitted for publication April 8, 1958.

From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Department Public Health Service.

Examination.—In the right eye accurate light projection was present. In the left eye corrected vision was 20/40. Gross examination was normal. The pupils reacted well to light and in accommodation, and ocular motility was normal. Biomicroscopy of the right eye showed the anterior segment to be normal. The anterior vitreous was "filled with cells," though these appeared slightly larger than inflammatory cells commonly seen. Dense veil-like opacities of wavy contour resembling "glass wool" were seen more posteriorly.

The anterior segment of the left eye was normal. The vitreous anteriorly contained a few cellular-appearing opacities and the same type of membranous "glass wool" opacities.

Visual fields were generally constricted in both eyes, and intraocular pressure was 23 mm. Hg (Schiøtz).

General physical examination revealed a small thyroid nodule, and several small posterior cervical lymph nodes could be palpated. On x-ray examination, there were cystic areas in the carpal bones of the left hand. Both maxillary antra and the inferior ethmoid sinuses appeared hazy, and "Schmorl's nodes" were seen in the lumbar spine. Intravenous pyelogram showed minimal blunting of the calyces, and abdominal film and gastrointestinal series suggested slight hepatomegaly. Nonspecific ST and T wave changes were present on electrocardiogram.

Routine hematology and urine examination were normal. The serum uric acid was

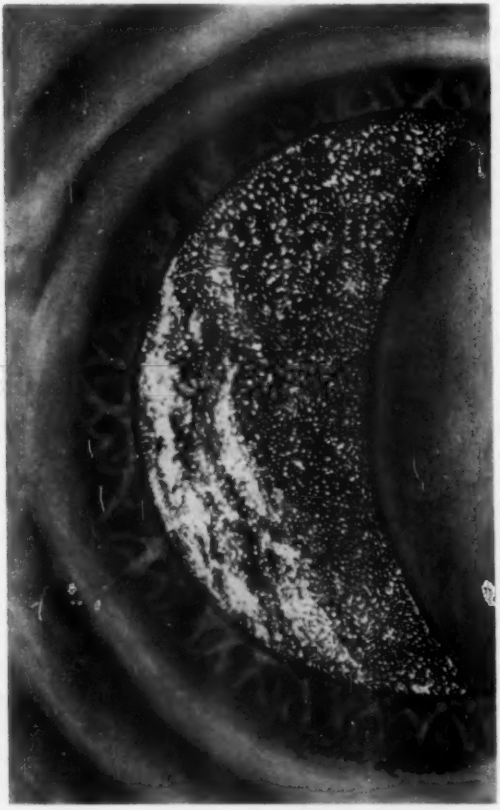

Fig. 2.—Drawing of the slit-lamp appearance of the vitreous of the right eye. (These drawings do not precisely convey the appearance of the opacities, but they are clearer than photographs.)

5.0 mg. %, and calcium, 10.4 mg. %; the total protein was 6.3 gm.; the albumin, 3.3 gm., and the globulin, 3.0 gm. %.

Routine electrophoresis was not notably abnormal, but analytical paper electrophoresis revealed a small abnormal α_2-component. Etiological work-up, including tuberculin, toxoplasmin, and Kveim skin tests, was negative.

Multiple biopsy specimens, including those from thyroid, lymph nodes, and skin, were positive for amyloid when stained with methylrosaniline chloride (methyl violet), cresyl violet, azan, periodic acid-Schiff (PAS), azure-eosin, ferric-ferricyanide, and aldehyde-fuchsin.

Treatment and Course.—Treatment with corticotropin (ACTH), 80 units for two days and 40 units per day thereafter for a month, brought no improvement. On Oct. 27, 1954, vitreous aspiration was attempted through a No. 20 needle, but no material was obtained. Early in 1955, pain developed in the right eye and a tension of 40 mm. Hg (Schiøtz) was found. Tonography done on Oct. 3, 1957, revealed a facility of outflow of 0.05 in the right eye. On gonioscopy the angle was completely open in both eyes.

Though tension was controlled with carbachol (Carcholin) 1.5% and neostigmine 5%, 2 drops O. U. five times a day, vision decreased to light perception O. D. and perception of hand movements O. S., and the vitreous opacities became more dense.

On Sept. 18, 1957, a vitreous transplantation was done in the left eye by transcleral incision and aspiration through a No. 16 needle, with subsequent replacement by bank vitreous. About 1.0 cc. of clear material was obtained, and no opacities were seen. Vision was essentially unchanged, and recovery was uneventful. The material removed was negative when stained for amyloid.

On Oct. 11, 1957, vitreous transplantation was attempted in the right eye and about 1.25 cc. of material containing stringy opacities was removed. Following this, there was slight improvement in light perception and projection. The opaque material stained strongly with Congo red, and stained metachromatically after formalin vapor fixation with methylrosaniline chloride and cresyl violet. The metachromatic staining was unaffected by treatment of the vitreous specimen with hyaluronidase before fixation, and monkey vitreous fixed and stained in the same manner did not stain as amyloid. Human bank vitreous containing a few small opacities was also fixed and stained in an identical manner but did not stain metachromatically or bind Congo red, confirming that the opacities removed from Case 1 were in fact comprised of amyloid.

Case 2.—The mother of patient 1, a 38-year-old housewife, was first seen on Feb. 28, 1944. In 1941, progressive fatigability, weakness, insomnia, intermittent diarrhea with tarry stools, and a gradual 30 lb. weight loss began. In 1942, nausea, vomiting, anorexia, and fecal incontinence developed and were soon followed by dizzy spells and weakness, coldness, numbness, and painful aching of the legs. The patient became unable to stand or walk; she was confined to bed and 2 weeks before admission, she suffered hematuria for 10 days. At about this time, scattered ecchymoses developed and her eyes became puffy and dark.

On examination the patient was emaciated and slightly febrile, with postural hypotension and numerous petechiae and ecchymoses.

Pupillary reactions were sluggish and the discs were ill-defined. (The fundi are not further described.) Cheilosis and atrophy of the tongue were present; the liver was 3 fingerbreadths below the right costal margin, and the spleen was 2 fingerbreadths below the left costal margin. Hemorrhages were present in the floor of the vagina, and the rectal sphincter was relaxed. Muscular wasting, though diffuse, was most prominent in the legs. Deep tendon reflexes were sluggish in the arms, and knee and ankle jerks were absent. Sensation was diminished or absent in the legs.

Laboratory investigation revealed a hematocrit of 24%. Segmental ileitis was seen on gastrointestinal series and scattered calcifications were present in chest x-ray. The tuberculin test was negative.

Shortly after discharge, the patient died at home and no postmortem examination was obtained, but biopsy specimens of skin and peripheral nerves showed amyloid on microscopic examination.

CASE 3.—The sister of patient 1 was a 32-year-old housewife, hospitalized first on May 25, 1953. Symptoms began two years previously with loss of all sexual desire, irregular menses, and a 40 lb. weight loss. Eighteen months before admission progressively severe nausea and vomiting began which, combined with severe diarrhea and constipation, soon debilitated her. Seventeen months before admission sharp shooting pains developed in the toes and heels, and six months before admission numbness of the fingers occurred, soon followed by profound weakness, inability to walk, and aching of the arms and legs. Gross hematuria developed seven months before admission, and memory loss and "blackout" spells occurred. Vision was blurred.

General physical examination was remarkable for postural hypotension, slight tachycardia, irregular pupils unreactive to light and only slightly reactive to accommodation, extreme muscle wasting with foot drop, sluggish reflexes and absent ankle jerks, and absence of pain sensation in the lower extremities. The spleen was at first felt 1½ fingerbreadths below the left costal margin but enlarged later to 3 cm. below the costal margin. The liver initially was not palpable, but later the lower border was felt 1 cm. below the right costal margin.

The eyes were prominent, and the orbital tissues became puffy. The pupils became totally unreactive, and all deep tendon reflexes disappeared. Laboratory studies revealed negative serological tests for syphilis. The hematocrit was 34%, and other laboratory studies were unremarkable except for a cerebrospinal fluid protein of 388 mg. %.

The diagnoses originally considered probable were tabes dorsalis, periarteritis nodosa, disseminated lupus erythematosus, vasculitis, diffuse carcinomatosis, and sarcoidosis. Diagnosis was confused by a second TPI test becoming positive. Later still, a routine syphilitic serology became positive but at this time the TPI test was negative.

The diagnosis of amyloidosis was confirmed by biopsy of the gum, muscle, saphenous nerve and skin; all of the specimens showed metachromatic amyloid deposits with equivocal staining by Congo red. The patient died on Jan. 4, 1956, and autopsy further confirmed the diagnosis.

Comment

Amyloidosis appears to have been described first by Rokitansky,[18] in 1842, and later elaborated upon by Virchow,[24] in 1855, and Wilks,[25] in 1856. Most patients with primary amyloidosis have been in their 50's though the disease occurs in all age groups. No special racial incidence has been noted; however, any studies of statistical distribution are rendered difficult, especially in the older literature, by the necessity to rule out diseases causing secondary amyloid deposition. Andrade[11] reported the first extensive series of the familial form of the disease in 1952. This has been confirmed by Kantarjian and De Jong[16] and by Rukavina et al.,[3] the latter authors finding the condition to be a simple Mendelian dominant.

The pathologic physiology of the disease is dependent on the widespread deposition of abnormal protein, Reimann et al.[26] regarding amyloidosis as a storage disease similar to the lipoidoses. Hass et al.[27-30] have demonstrated that glucosamine may comprise 1.5% of the amyloid, and they have further delineated the composition of amyloid. This is variable, however, and as yet not clearly determined.

Though foreign-body giant cells may be present around amyloid deposits, and though secondary amyloidosis has been reported to

regress,[31-32] regression of primary amyloidosis has not been reported.

Kuczynski's [33] experimental production of amyloidosis in mice, by feeding diets rich in casein, points out the relationship between amyloidosis and protein metabolism. King and Oppenheimer [34] have noted a high consumption of dairy products in the history of some patients with amyloidosis, but this has not been confirmed or clarified. Jaffe [35] suggested that primary amyloidosis might be a phenomenon of protein allergy. Others also have suggested an immunological or autosensitization etiology of the disease and have correlated amyloid deposition with hyperglobulinemia and with the collagen diseases.[7,36] There is no evidence to implicate this in the familial form of the disease.

Peräsalo and Latvalahti [39,40] found that corticotropin and cortisone increased the development of experimental amyloidosis as did castration and thyroidectomy. This is borne out by clinical experience of some,[10,41-44] though disputed by others.[45]

The diagnosis of amyloidosis, once suspected, is best confirmed by biopsy, though affected tissue may not be contained in all biopsy specimens. Gum biopsy is popular [46] but skin, sternal marrow, and kidney biopsies have proved helpful. Liver or spleen biopsy, found useful by some,[47] may lead to rupture of the organ and fatal hemorrhage.[48]

The congo red test is positive less often in primary than secondary amyloidosis, and interpretation, though difficult, may be diagnostically helpful.[49] In 1954 Gilliland and Stanton [50] emphasized the importance of elevated α_2-globulin as seen on paper electrophoresis and reported that the albumin/α_2-globulin ratio may be diagnostically helpful. Letterer and Schneider,[51] however, suggest that the α_2-globulin increase is not specific for amyloidosis, but rather reflects dysproteinemia.

In 1956 Rukavina et al.[3] noted both abnormal lipoprotein fractions and an abnormal type of β_2-globulin in one family with primary amyloidosis. A similar abnormal β_2-globulin is reported in Case I, who is not related to the family which these investigators reported.

The clinical symptomatology of primary amyloidosis is often bizarre and nonspecific, involving multiple systems. It is expertly discussed and reviewed by Symmers [2] and by Rukavina et al.,[3] and the pathologic anatomy, especially of the nervous,[9-11,13,16,19,20,23,52-55] cardiac,[1,7,21,37,38,56] gastrointestinal,[22,57-59] and genitourinary [1,12,55,57-59] symptoms has been clearly described.[1]

Ocular symptomatology is reported to occur in 8.4% of all cases of primary amyloidosis,[3] but reliable figures are not available for the familial type alone. These symptoms may include proptosis, ptosis, thickening of the lids, or hemorrhage into the lids, conjunctiva, sclera, or retina.[4-23] Ocular palsies and pupillary abnormalities are reported, and direct involvement of the optic nerve has been documented.[4]

Previously, ocular pain and unexplained blindness have been reported in patients with amyloidosis [59,61] but glaucoma has not been discussed or documented in these cases. The occurrence of glaucoma in a 25-year-old man with primary familial amyloidosis suggests that the systemic disease also plays a part in the genesis of the glaucoma. It is tempting to hypothesize that, in the absence of obvious protein in the aqueous, infiltration of outflow channels may be present, but the response to miotics cannot thereby be explained. No pathological evidence is available as to the site of outflow obstruction.

Once the diagnosis of primary amyloidosis is considered, a definitive diagnosis is often not difficult. Case 1 illustrates that ocular symptoms may be the most striking, or even the only symptomatic, manifestation of the disease. Even when ocular abnormalities are not noted until the systemic disease is advanced, ocular signs such as lid ecchymosis and "glass wool" vitreous opacities may suggest the correct diagnosis.

Vitreous opacities were described as part of the syndrome of primary familial amy-

loidosis in 1953 by Kantarjian and De Jong,[16] and the possibility of their diagnostic specificity was considered in 1955 by Falls.[17] Previous to this, "iritis" and "iridocyclitis" were diagnosed in patients with secondary amyloidosis; however, the ocular findings were not described.[60,61]

The opacities, which may suggest in their appearance that globules of material have been deposited on the normal vitreous fibers, may seem at first to be cellular. If such opacities are present in the absence of anterior inflammation, however, the diagnosis of amyloidosis may be suspected. The demonstration that the opacities are comprised of amyloid lends further support to the assumption that they are a specific manifestation of the general disease and may clarify the diagnosis in an otherwise obscure case.*

Summary

Three new cases of primary familial amyloidosis are reported. One of these presented with blindness as his only symptom, and there were veil-like "glass wool" vitreous opacities in the absence of cells or flare in the anterior chamber. Though these opacities may superficially appear cellular, they are sufficiently distinctive to suggest the correct diagnosis. The diagnostic specificity of the vitreous abnormalities was confirmed by vitreous aspiration and demonstration that the opacities were comprised of amyloid.

The ocular symptomatology of amyloidosis is reviewed, and glaucoma is documented in association with this condition. An abnormal α_2 globulin, similar to that which Rukavina et al.[3] found, has been documented in a case unrelated to the family they studied.

Patient No. 3 was seen at the Johns Hopkins Hospital, and a summary of the history was furnished by Dr. L. Shulman. Patient No. 2 was seen at the University of Virginia Medical Center. Dr. S. Weissman did the serum electrophoresis on Case I.

Ophthalmology Branch, National Institutes of Health (14).

* Since this manuscript was submitted, Case 1 has developed ecchymosis of the lids, paresthesias, and a right ulnar nerve neuropathy.

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Evaluation of Absorbable Gelatin Film (Gelfilm) in Cyclodialysis Clefts

Part I

DAVID BARSKY, M.D., and ROBERT A. SCHIMEK, M.D., Detroit

When surgery is indicated in the management of glaucoma, the cyclodialysis operation provides an internal drainage mechanism which is thought by some to resemble most closely the physiologic state.[1] However, failure of the cleft to remain patent sometimes leads to an unsuccessful operation. In the past, foreign materials of many types,[2-4] magnesium, gold, platinum, stainless steel, etc., have been advocated as implants to keep the cleft open, but generally these have caused undue amounts of inflammatory reaction. The ideal substance to maintain patency of the cleft should be nonantigenic and should not give rise to severe inflammatory reaction; it should be absorbable but should be absorbed slowly enough to keep the cleft open while the postoperative reaction and hyphema subside. Except for its rather rapid absorption, an air bubble fulfills these requirements.[5] However, in cases where fibrosis is more marked postoperatively an air bubble is often inadequate.

Gelfilm is a nonantigenic, absorbable gelatin film.[6-8] The rate of absorption of this gelatin film varies in different tissues[9,10]; subconjunctival implants require two or three months to absorb. When dry, absorbable gelatin film looks and feels like brittle plastic; when moistened it becomes soft and pliable, yet still slightly elastic, and can be cut into any shape or can be molded around irregular surfaces.

Absorbable gelatin film has been used in extraocular muscle surgery and in diathermy operations for retinal detachments, to limit the amount of adhesions formed postoperatively. It has also been used in iridencleisis and trephine operations for glaucoma.[11] With these data available, it seemed logical to try absorbable gelatin film in cyclodialysis clefts.

In the experiments reported herein, 15 albino rabbits were used as test animals. Routine cyclodialysis, with air bubble, was performed on the right eyes of 10 of these rabbits, and cyclodialysis with absorbable gelatin film insert was performed on the left eyes of all 15. The rabbits were anesthetized with pentobarbital (Nembutal) intravenously and retrobulbar injection of 2% lidocaine (Xylocaine). An incision was made through the conjunctiva superiorly, about 6 mm. from the limbus, in the 12 o'clock position. At this point, a scratch incision 3 mm. long was made obliquely in the sclera and a preplaced 000000 black nonabsorbable surgical (silk) suture was then inserted through the conjunctiva and sclera. This was looped out of the incision site and laid aside. A cyclodialysis spatula was inserted and passed forward into the anterior chamber, detaching the ciliary body from the sclera in a sweep from 10 o'clock to 2 o'clock. In the right eyes of 10 rabbits an air bubble was introduced, filling one-half of the chamber; in the left eyes of 11 rabbits a thin strip of absorbable gelatin film was doubled over a specially made cyclodialysis spatula-introducer (Figs. 1 and 2) and then inserted into

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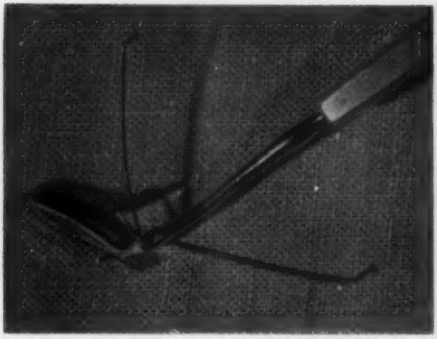

Fig. 1.—Cyclodialysis spatula-introducer with absorbable gelatin film (open). Reduced about 40% from mag. × 2.

Fig. 2.—Cyclodialysis spatula-introducer with absorbable gelatin film (closed). Reduced about 40% from mag. × 2.

the ready-formed cleft, so that the gelatin film appeared in the angle of the anterior chamber. The double gelatin film strip thus formed a V, with the apex at the chamber angle and the two limbs of the V spreading the cleft apart posteriorly by the innate elasticity of the gelatin film. Alternatively, in the left eyes of four of the rabbits a single gelatin film strip was inserted. The redundant portion of the gelatin film at the scleral incision was then cut off flush, and the preplaced suture was tied.

Results

Absorbable gelatin film strip inclusion in cyclodialysis was performed on the left eyes of 15 rabbits. Either a double or a single gelatin film strip was inserted. In 10 of the rabbits a routine cyclodialysis with air injection was performed on the right eye, while in the other 5 rabbits the right eye was not operated upon at all. It should be noted that the cyclodialysis operation is somewhat more traumatic in rabbits than in humans because of the strong pectinate ligaments (Fig. 3).

The rabbits were killed at intervals ranging from 2 to 16 weeks, following which the eyes were studied histologically.

Clinically, hyphema occurred in almost all cases postoperatively, filling about one-half the anterior chamber. This usually cleared within one week. Perilimbal injection persisted for a little more than a week

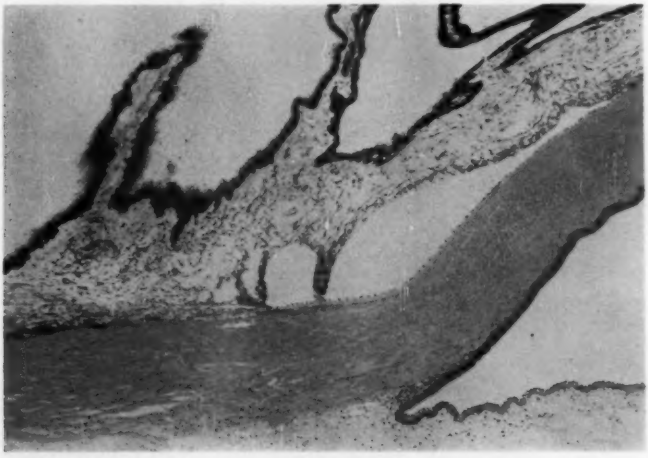

Fig. 3. — Photomicrograph of normal anterior chamber angle in albino rabbit. Note thick pectinate ligaments. Reduced about 39% from mag. × 150.

in the control eyes and for several weeks in the eyes containing gelatin film. In most cases the cornea remained cloudy at the operative site for at least six weeks or longer, and it was evident that Descemet's membrane had been stripped here. The anterior chamber continued to show a few cells and a 1+ ray even up to three months in the gelatin-film-treated eyes, in contrast to the control eyes, which usually cleared completely within a few weeks. One case with gelatin film showed definite posterior synechiae at the end of three months. The iris vessels remained engorged and dilated at the site where the gelatin film was inserted. The tonometer readings were too inconsistent to afford reliable evidence, although there seemed to be no real difference in the tension readings between the control eyes and those with gelatin film. Gonioscopy was performed on five of the eyes wherein absorbable gelatin film had been inserted. In two of these, the cleft appeared to be open at the site of the gelatin film but was bounded by peripheral anterior synechiae; in the other cases, no cleft was visible.

Microscopic sections revealed the following data. (It should be noted that absorbable gelatin film stains deeply basophilic initially but as it is absorbed it tends to become eosinophilic. In stained sections, it is relatively easy to identify the absorbable gelatin film even grossly.)

I. In all the control eyes operated on, the cleft was closed with only slight fibrosis.

II. In the eyes wherein absorbable gelatin film was used the findings were as follows:

(1) After two weeks (one eye): The cleft was patent with a double strip of gelatin film in the cleft. There was marked chronic inflammation and fibrosis. (Fig. 4).

(2) After three weeks (four eyes): In two eyes, no gelatin film was seen and the cleft was closed. In a third eye, the gelatin

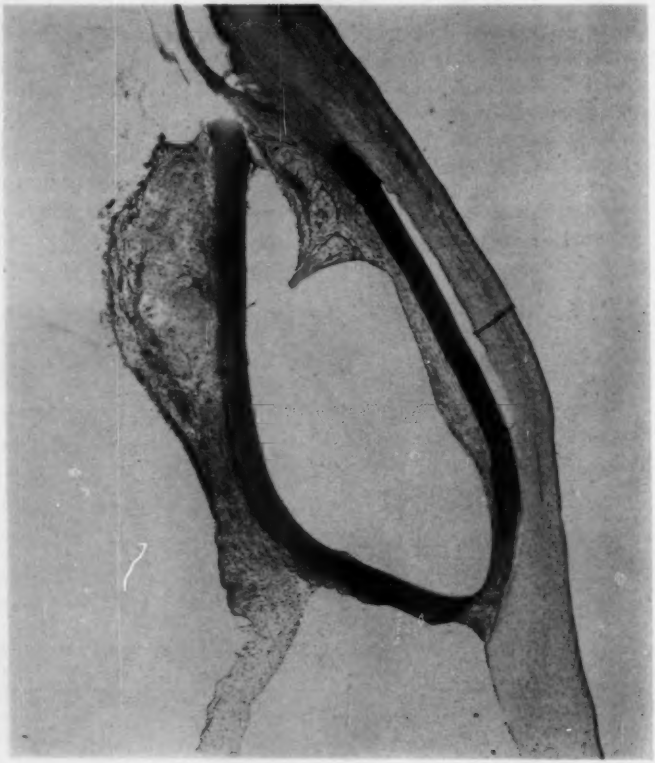

Fig. 4. — Photomicrograph of doubled absorbable gelatin film strip in cyclodialysis cleft after two weeks. Note marked fibrosis; × 26.

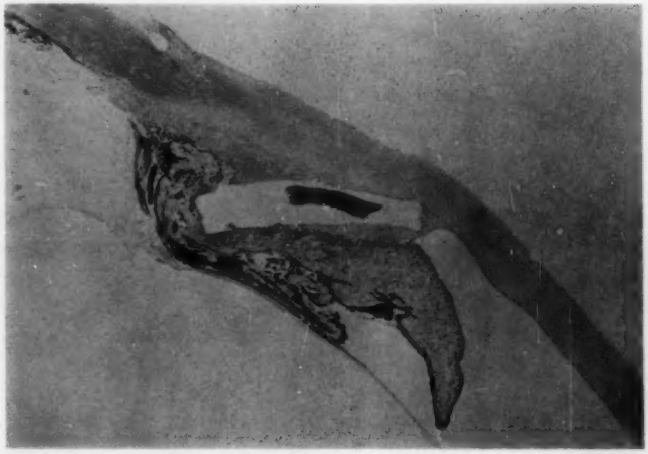

Fig. 5. — Photomicrograph of closed cyclodialysis cleft with absorbable gelatin film strip in anterior chamber bounded by anterior synechiae after three weeks. Reduced about 39% from mag. × 26.

film strip was found in the anterior chamber, bounded by anterior synechiae. The cleft was closed (Fig. 5). In the fourth eye, a small bit of gelatin film was seen to be present in the suprachoroidea, surrounded by marked chronic inflammatory reaction, and the cleft was closed.

(3) After four weeks (one eye): A double strip of gelatin film was present, holding the cleft open in a spring-like fashion, separating the iris and ciliary body away from the sclera. There appeared to be marked fibrosis of the cornea and iris where gelatin film was in contact, as well as chronic inflammatory reaction around the gelatin film in the region of the pars plana (Figs. 6 to 10).

(4) After 6, 8, 10, 12, and 14 weeks (seven eyes): No cleft was seen and no gelatin film, except for some gelatin film remnants seen on the posterior cornea in the 12-week eye.

(5) After 16 weeks (one eye): The cleft was open but lined by fibrous tissue. A strip of gelatin film was seen in the cleft in the clear space between the ciliary body and sclera. There was moderate chronic inflammatory reaction locally.

Thus, absorbable gelatin film was found in the cleft, on section, in only three cases. One

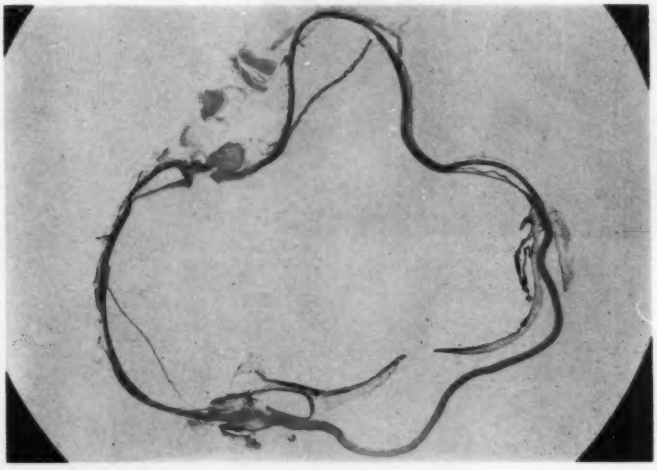

Fig. 6. — Photomicrograph of entire globe, demonstrating doubled absorbable gelatin film strip in cyclodialysis cleft after four weeks. Reduced about 39% from mag. × 5.5.

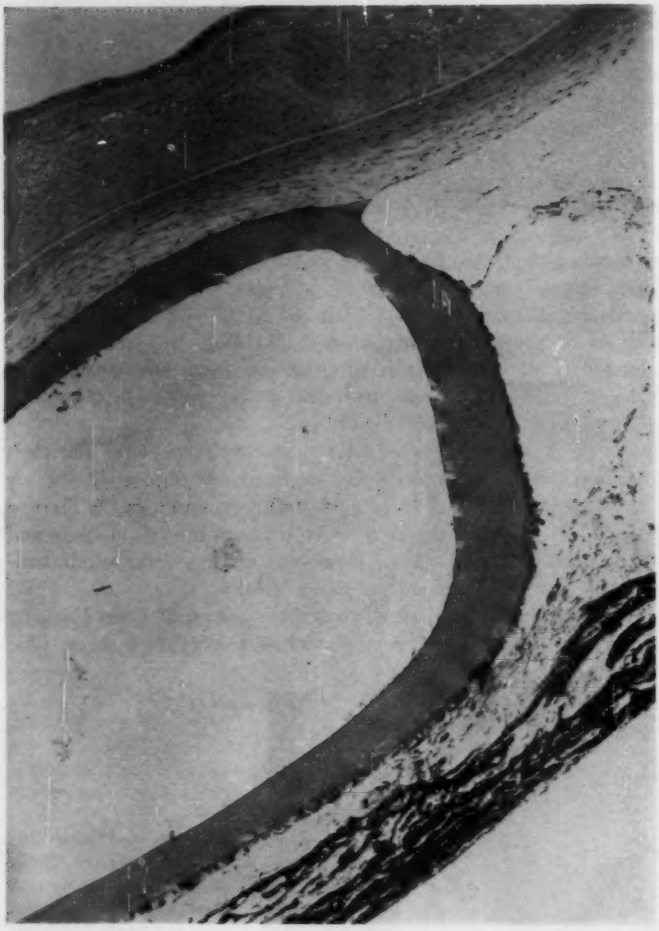

Fig. 7. — Absorbable gelatin film strip holding cleft open in a spring-like manner at the angle. Note marked fibrosis on posterior corneal surface after four weeks. Reduced about 15% from mag. × 105.

Fig. 8. — Inflammatory reaction to absorbable gelatin film in ciliary body area after four weeks. Reduced about 15% from mag. × 105.

Fig. 9. — High-power view of inflammatory reaction to absorbable gelatin film after four weeks. Reduced about 15% from mag. × 450.

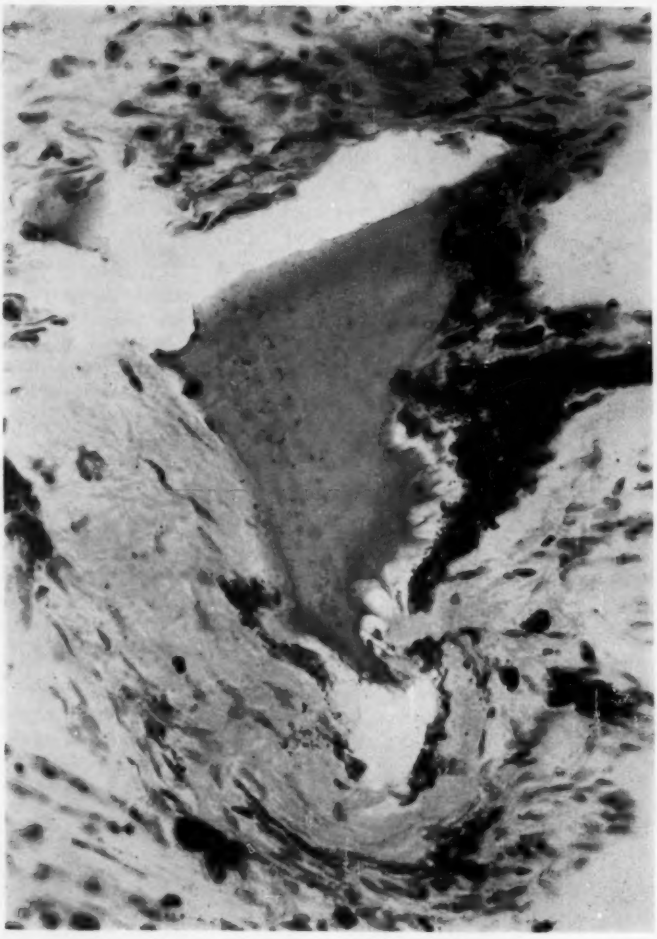

Fig. 10. — High-power view of inflammatory reaction surrounding absorbable gelatin film fragment after four weeks. Reduced about 15% from mag. × 450.

eye removed after 2 weeks, another after 4 weeks, and a third after 16 weeks, showed a patent cleft with gelatin film. All other eyes showed no cleft remaining.

Summary and Conclusions

Absorbable gelatin film (Gelfilm) was used in cyclodialysis in 15 rabbit eyes. In three cases, one at 2 weeks, one at 4 weeks, and one at 16 weeks, the absorbable gelatin film was present on microscopic section and the cleft appeared patent but lined by fibrous tissue. In all other cases the cleft was closed. In the 10 control eyes the cleft was closed. The chronic inflammation and scarring seen in the cases operated on was increased where absorbable gelatin film was inserted. This might be due, in part, to the technical trauma of inserting the absorbable gelatin film. However, the eyes with absorbable gelatin film remained injected and showed a mild iritis longer than the control eyes: It would seem in order to conclude that absorbable gelatin film is not entirely inert within the eye. On the basis of this experiment alone, absorbable gelatin film cannot be recommended for cyclodialysis because (1) considerable trauma is involved in the complex technique of insertion; (2) intraocular reaction is prolonged, and fibrosis is prominent; (3) the gelatin film does not consistently hold the cleft open.

Dr. James R. Duke, of the Pathology Department of Wilmer Eye Institute, and Dr. W. S. Davies, of the Pathology Department of Kresge Eye Institute, contributed the services of their departments to make the histologic studies possible.

Department of Ophthalmology, Henry Ford Hospital (2).

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Evaluation of Dichlorphenamide as an Ocular Hypotensive Agent

R. A. SCHIMEK, M.D.; J. V. BALIAN, M.D.; F. J. LEPLEY, M.D., and J. A. OTTUM, M.D., Detroit

Introduction

The recent developments of new carbonic anhydrase inhibitors have stimulated interest in the possibility of their use as ocular hypotensive agents. The clinical and experimental value of the carbonic anhydrase inhibitor acetazolamide in lowering intraocular pressure has already been proved.[1-5] It follows that the newer agents might also have similar ocular pharmacologic action. Dichlorphenamide and chlorothiazide (Merck Sharp & Dohme) were chosen for experimental investigation in this study.

Chemical Description

Dichlorphenamide is a dichlorinated benzenedisulfonamide. Its chemical name is 1,3-disulfamyl-4,5-dichlorobenzene. The drug is a weak dibasic acid and is said to be soluble in dilute solutions of sodium carbonate and sodium hydroxide, stable at room temperature. In vitro, dichlorphenamide has been reported as approximately 30 times as effective an inhibitor of carbonic anhydrase as acetazolamide and 300 times as effective as sulfanilamide.[6] It has been found to increase sodium excretion of the kidney in dogs and also to increase the excretion of potassium and bicarbonate ions. Therefore, it characteristically produces an alkaline urine. Unlike acetazolamide, it causes a definite increase in chloride excretion, so that it tends to produce less marked metabolic acidosis than acetazolamide in equivalent dosages. The drug is well and promptly absorbed orally and is essentially as active orally as parenterally. Dichlorphenamide has not been observed to have important pharmacodynamic side-effects. Toxicity studies in dogs have revealed no significant toxic side-effects after daily administration of the drug for as long as three months. In humans, the side-effects of dichlorphenamide chiefly parallel those found with acetazolamide administration.[6]

Chlorothiazide is chemically designated as 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. It is a dibasic acid and is readily soluble at a pH greater than 7.5. In vitro this compound is approximately 10 times as effective an inhibitor of carbonic anhydrase as sulfanilamide.‡ In animals the drug causes a marked increase in the renal elimination of sodium and chloride and a smaller increase in the excretion of potassium and bicarbonate. Sodium and chloride are excreted mole for mole. Like dichlorphenamide, the drug is less prone to produce metabolic acidosis. It is well absorbed orally and equally as effective by oral or parenteral route of administration. Chronic toxicity studies in rats and dogs have been continued for six months without significant side-effects.[7,8] Recent studies have shown that this drug is effective in lowering blood pressure in essential hypertension.[9]

Experimental Studies

The evaluations and the experimental methods used in this analysis (except for the preliminary phase) were arrived at after considerable time had been spent eliminating bias and achieving an adequate control system for the determinations.

All rabbits were fed commercial Purina Rabbit Pellets, and this was supplemented

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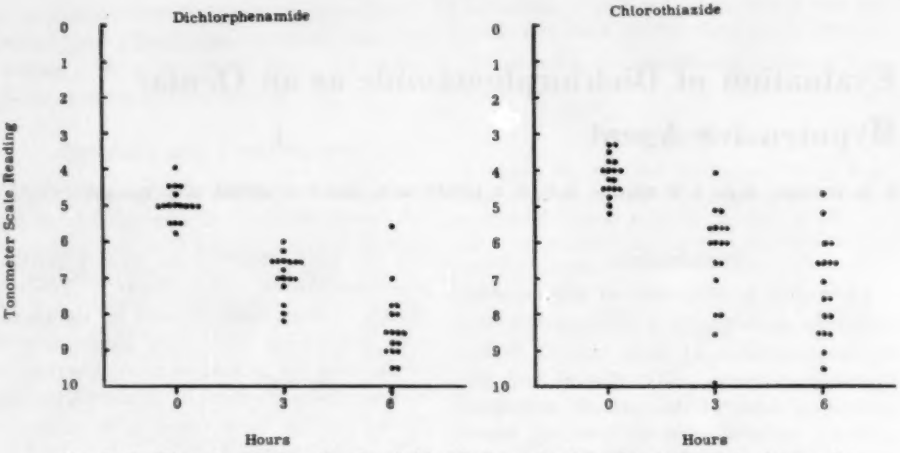
From the Department of Ophthalmology of the Henry Ford Hospital.

‡ Merck Sharpe & Dohme Research Laboratory.



Graph 1 (Experiment 1).—Graph of biased data showing the decrease in intraocular tension following dichlorphenamide and chlorothiazide administration, which later experiments proved invalid. No rabbits were used exclusively as controls. Each dot represents the average of the tonometer readings of both eyes of one rabbit.

with fresh lettuce and carrots. The rabbits were allowed free access to the food at all times.

In Experiment 1, intraocular tensions were determined with a Schiøtz tonometer 8 or 10 years old which had been made by Mueller. In the remaining experiments, all tensions were determined with a brand new Sklar tonometer. In either event, tensions were measured with a 5.5 gm. weight after instillation of proparacaine (Ophthaine*) in the conjunctival sac of each rabbit eye. The rabbits were otherwise unanesthetized and were held manually. The eyelids were then held open by the person measuring the tension, and care was exercised to be certain that the nictitating membrane rode above the footplate of the tonometer.

EXPERIMENT 1.—The preliminary phase of the experiment, to evaluate the intraocular tension-lowering effects of dichlorphenamide and chlorothiazide, was performed with use of 18 New Zealand White rabbits having an average weight of approximately 2.1 kg. However, the results of this evaluation were biased, as shown by subsequent more carefully controlled studies. This study was performed as follows: To evaluate the baseline intraocular pressure of the individual rabbit eyes, determinations of intraocular pressures were made on each rabbit at the beginning and end of a 24-hour interval. After 4 days the pressures were again determined 24 hours apart (at the same time of day as previously) and this was followed immediately by the oral administration of dichlorphenamide, 100 mg. per kilogram, to all rabbits. No controls were utilized in this preliminary phase. Tonometric measurements at three hours and six hours after the administration of this drug appeared to show a very marked lowering of intraocular pressure in all cases. The same experiment was then repeated with chlorothiazide, with use of the same dosage and the same intervals between the measuring of intraocular pressures. The results again appeared to indicate a marked lowering of intraocular pressure (Graph 1).

EXPERIMENT 2.—In order to eliminate the possibility of these lower tension measurements being due to factors other than the drugs themselves (especially to subconscious bias on our part, since we knew that there were no controls and that all rabbits were receiving a potentially ocular hypotensive

*E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York.

TABLE 1 (EXPERIMENT 2).—*Method of Selection of Rabbits for Drug Administration Utilizing the Roman Square Design* *

Rabbit No.	Run 1	Run 2	Run 3	Run 4	Run 5
Group 1					
1	Control	Dichlorphenamide	Acetazolamide	Control	Chlorothiazide
2	Chlorothiazide	Acetazolamide	Control	Control	Dichlorphenamide
3	Dichlorphenamide	Control	Control	Chlorothiazide	Acetazolamide
4	Acetazolamide	Control	Chlorothiazide	Dichlorphenamide	Control
5	Control	Chlorothiazide	Dichlorphenamide	Acetazolamide	Control
Group 2					
6	Control	Dichlorphenamide	Acetazolamide	Control	Chlorothiazide
7	Chlorothiazide	Acetazolamide	Control	Control	Dichlorphenamide
8	Dichlorphenamide	Control	Control	Chlorothiazide	Acetazolamide
9	Acetazolamide	Control	Chlorothiazide	Dichlorphenamide	Control
10	Control	Chlorothiazide	Dichlorphenamide	Acetazolamide	Control

* Two groups of five rabbits were used, and the drugs were administered a total of five times to each group.

drug), a second experiment utilizing Roman square designs was set up (Table 1). In this design, two Roman squares were utilized, with five rabbits in each square. In this experiment, one of us administered the drugs, and two others measured and recorded the intraocular tensions without knowing which rabbits received the drugs and which did not. In each "run," two rabbits served as controls, one rabbit received dichlorphenamide, one rabbit received chlorothiazide, and one rabbit received acetazolamide. Preliminary tensions were determined in all rabbits prior to administration of the drugs. After drug administration, tension determinations were repeated at intervals of three and six hours. When two days had elapsed, the next "run" was made, with different rabbits receiving or not receiving the drugs. A total of five "runs" were made. Again, the drugs were administered orally, with a dosage of 100 mg. per kilogram for all drugs used. The New Zealand White rabbits used in this and subsequent experiments had an average weight of approximately 1.1 kg. and were younger than those used in the preliminary experiment. Results of this experiment showed no

TABLE 2 (EXPERIMENT 3).—*Intraocular Tensions Grouped According to the Drug Administered* *

	Av. Tonometer Scale Reading								
	−28 Hr.	−18 Hr.	0 Hr.	+3 Hr.	+6 Hr.	+30 Hr.	+54 Hr.	+78 Hr.	+126 Hr.
Group 1									
Dichlorphenamide	2.6	2.6	2.7	3.3	3.2	3.1	3.2	3.3	3.3
Chlorothiazide	2.6	2.7	2.9	3.2	3.5	3.7	2.1	2.5	3.1
Acetazolamide	3.4	3.1	2.5	3.4	2.9	3.5	3.0	3.0	3.6
Control	2.7	2.7	2.8	3.0	3.6	3.2	3.3	3.1	3.2
Group 2									
Dichlorphenamide	2.6	2.3	2.8	3.3	3.0	2.9	3.0	3.1	3.4
Chlorothiazide	2.6	2.9	2.8	3.4	3.1	3.0	3.1	3.4	3.7
Acetazolamide	3.1	2.8	3.0	3.3	3.0	3.0	2.8	2.8	2.9
Control	2.4	2.4	2.4	2.6	2.9	2.5	2.4	2.8	2.8
Group 3									
Dichlorphenamide	2.8	2.5	2.7	3.5	2.7	3.2	2.8	2.9	2.6
Chlorothiazide	2.6	2.3	2.5	2.9	3.4	2.6	3.0	2.6	2.6
Acetazolamide	2.6	2.5	2.9	3.4	3.0	2.5	3.6	2.9	2.3
Control	2.5	2.5	2.2	3.0	2.7	2.7	2.7	2.4	2.7

* Each figure in the table represents the average tonometer scale readings on all rabbits receiving the drug for five "runs" (10 eyes). The control figures represent the average readings on all control rabbits for five "runs" (20 eyes). The drugs were administered orally immediately after the zero hour tonometer readings.

TABLE 3 (EXPERIMENT 3).—*Average Intraocular Tensions for the Three Groups in Table 2**

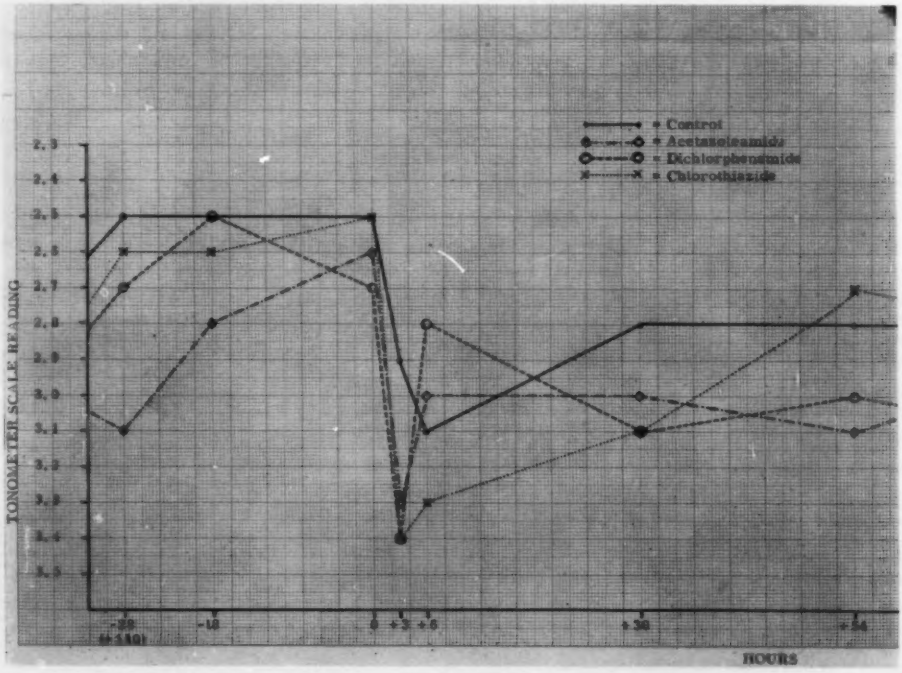
	Tonometer Scale Reading, Av. of 3 Groups								
	−28 Hr.	−18 Hr.	0 Hr.	+3 Hr.	+6 Hr.	+30 Hr.	+54 Hr.	+78 Hr.	+126 Hr.
Dichlorphenamide	2.7	2.5	2.7	3.4	2.8	3.1	3.0	3.1	3.1
Chlorothiazide	2.6	2.6	2.7	3.4	3.3	3.1	2.7	2.8	3.1
Acetazolamide	3.1	2.8	2.6	3.3	3.0	3.0	3.1	2.9	2.9
Control	2.5	2.5	2.5	2.9	3.1	2.8	2.8	2.8	2.9

* Each figure on rabbit receiving the drugs represents an average tonometer reading for 30 rabbit eyes. The control figures represent an average reading for 60 eyes.

significant effects on intraocular pressure resulting from any of the drugs.

EXPERIMENT 3.—After the first two attempts at evaluation of the drugs, further refinement of the experimental design seemed desirable. A third experiment was carried out, utilizing 15 rabbits. The experimental design was in the form of three five-by-five Roman squares, with use of an interval of seven days between runs. The methodology was exactly the same as in the previous experiment except that (1) three groups were used; (2) instead of a two-day interval between administration of drugs, one week was allowed to elapse; (3) tonometry readings were taken more often before and after the times for drug administration than had been the case in Experiment 2. Again, in each "run" there were two controls, and one rabbit received dichlorphenamide; one, chlorothiazide, and one, acetazolamide. The data from Experiment

Graph 2 (Experiment 3).—Comparison of the effect of oral administration of acetazolamide,



3 are summarized in Tables 2 and 3 and Graph 2. These data show no significant effect on intraocular pressure in the normal rabbit eye resulting from any of the three drugs.†

EXPERIMENT 4.—In view of the work of Becker,[10] showing that administration of adrenal steroids, especially fludrocortisone acetate (9α-fluoro-17-hydroxycorticosterone-21-acetate), prevents the compensatory decrease in outflow facility of rabbits which may occur following acetazoleamide administration, it was decided to begin a fourth experiment, using this steroid, to assure that our rabbits were "responsive" to this type of hypotensive agent and were not the so-called "pseudoresistant" type. In this experiment a smaller number of rabbits was utilized and only one of the drugs, dichlorphenamide, was tested.

Ten New Zealand White rabbits were studied in four consecutive trial periods, and each trial period was separated by 48 hours. Each rabbit alternated between receiving the drug during one trial period and not receiving it in the next (Table 4). Intraperitoneal injections of fludrocortisone were given to all rabbits 30 minutes prior to the administration of dichlorphenamide. Control tensions were determined immediately prior to the steroid injections and prior to the drug administration. Dichlorphenamide was given intraperitoneally, 100 mg. per kilogram, to those rabbits selected to receive the drug during any particular trial period. Determination of intraocular tension was then repeated on all eyes one hour after drug administration. The person measuring the tensions was unaware of which rabbits re-

† Statistical determination of the probability among the four groups (control, dichlorphenamide, chlorothiazide, and acetazolamide) of the differences between 0-hour and +3-hour readings, by the usual methods of analysis of variance, revealed $P \sim 0.10$.

dichlorphenamide, chlorothiozide on the intraocular tension of rabbits. Data from Table 3.

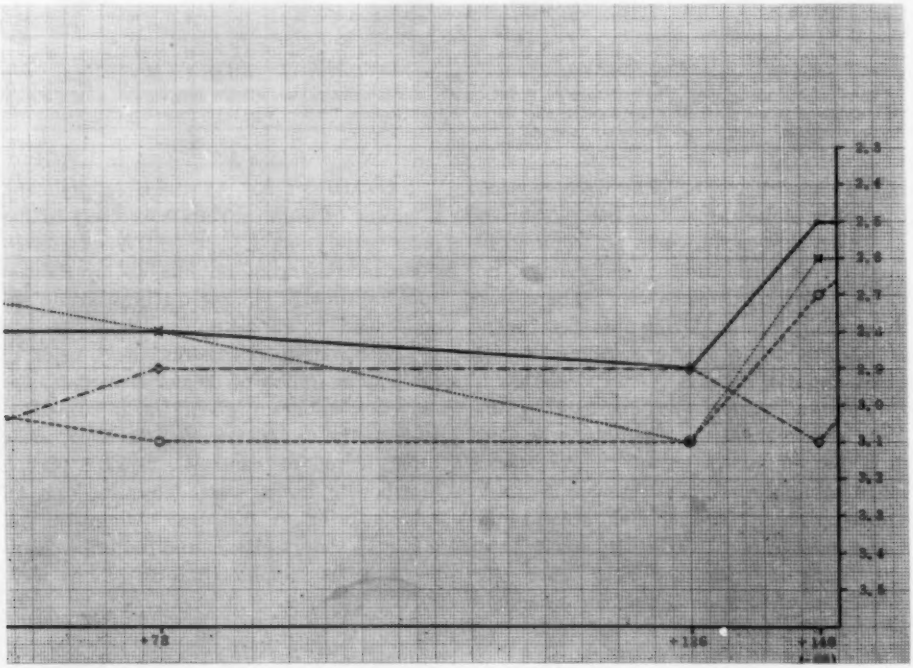


TABLE 4 (Experiment 4).—*Data Showing the Effect of Parenteral Dichlorphenamide Administration on the Intraocular Tension of Rabbits Receiving Fludrocortisone* *

		Intraocular Tension, Tonometer Scale Units														
		Run 1			Run 2			Run 3			Run 4			Run 5		
Rabbit No.	Eye	−30 Min.	0 Min.	+60 Min.	−30 Min.	0 Min.	+60 Min.	−30 Min.	0 Min.	+60 Min.	−30 Min.	0 Min.	+60 Min.	−30 Min.	0 Min.	+60 Min.
		Dichlorphenamide			Control			Dichlorphenamide			Control			Dichlorphenamide		
1	R. E.	2	2	3	x	x	x	x	x	x	x	x	x	x	x	x
	L. E.	2	2	3	x	x	x	x	x	x	x	x	x	x	x	x
		Dichlorphenamide			Control			Dichlorphenamide			Control			Dichlorphenamide		
2	R. E.	3	2	3	x	x	x	x	x	x	x	x	x	x	x	x
	L. E.	2	3	2	x	x	x	x	x	x	x	x	x	x	x	x
		Control			Dichlorphenamide			Control			Dichlorphenamide			Control		
3	R. E.	2	2	2	2	3	5	2	4	5	2	3	3	3	3	2
	L. E.	2	2	3	2	4	5	4	4	5	3	3	4	3	3	2
		Dichlorphenamide			Control			Dichlorphenamide			Control			Dichlorphenamide		
4	R. E.	2	2	3	2	3	2	5	6	5	4	4	4	4	4	4
	L. E.	3	3	3	2	2	2	5	4	4	3	3	3	3	3	4
		Dichlorphenamide			Control			Dichlorphenamide			Control			Dichlorphenamide		
5	R. E.	2	3	2	3	3	3	2	4	7	3	4	4	4	3	4
	L. E.	2	2	2	3	3	3	1	4	6	2	3	4	3	3	4
		Control			Dichlorphenamide			Control			Dichlorphenamide			Control		
6	R. E.	2	2	3	2	3	3	5	2	1	3	3	4	3	3	3
	L. E.	2	3	3	2	2	2	6	2	2	2	4	5	3	3	3
		Dichlorphenamide			Control			Dichlorphenamide			Control			Dichlorphenamide		
7	R. E.	2	2	4	3	3	4	2	3	9	2	4	3	x	x	x
	L. E.	2	3	3	2	4	4	3	4	9	3	3	3	x	x	x
		Control			Dichlorphenamide			Control			Dichlorphenamide			Control		
8	R. E.	2	3	3	2	3	5	5	5	5	2	3	6	3	3	4
	L. E.	3	3	3	2	4	5	5	6	5	4	4	6	4	3	4
		Control			Dichlorphenamide			Control			Dichlorphenamide			Control		
9	R. E.	3	2	2	2	2	3	3	4	3	3	3	5	4	4	4
	L. E.	2	3	2	2	2	3	5	3	3	4	3	5	4	4	5
		Control			Dichlorphenamide			Control			Dichlorphenamide			Control		
10	R. E.	2	2	2	2	3	4	2	2	2	3	2	4	4	3	2
	L. E.	2	3	2	2	3	5	3	2	3	3	2	5	4	3	2

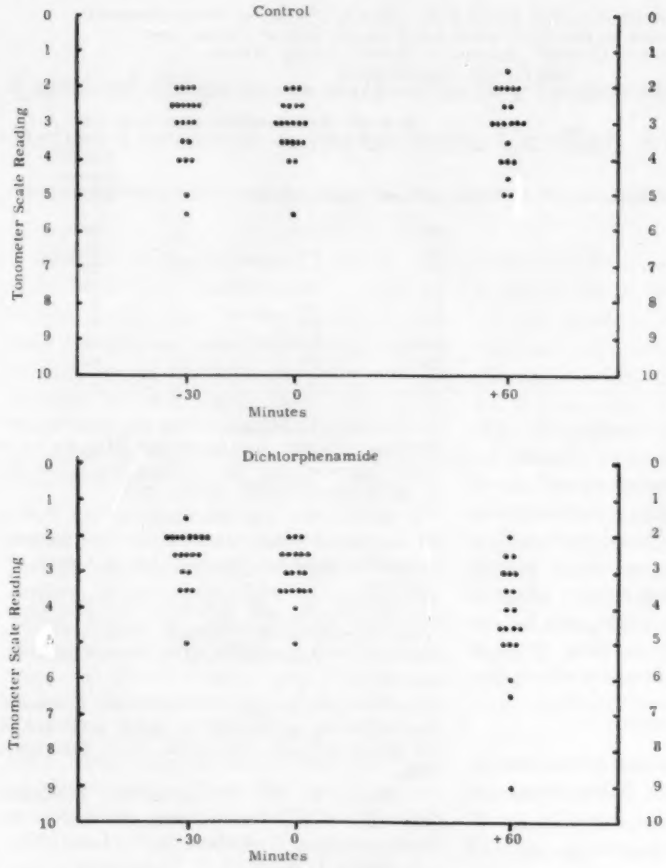
* Rabbit deaths are represented by x in the table. Fludrocortisone was administered immediately after the −30-minute tension. Dichlorphenamide was administered immediately after the zero-minute tension. Tensions were again determined 60 minutes after dichlorphenamide administration (+60-minute tension).

ceived the drug. The data were recorded by a second person, and so the person who measured the tension could not refer to his previous determinations and could not identify any particular rabbit. There were three rabbit deaths during this experiment, none of which could be attributed to administration of the drug.

Statistical analysis of the data of this experiment (Table 4 and Graph 3) revealed that the administration of fludrocortisone itself had no significant effect upon the intraocular tension. However, the data did indicate a significant ($P \sim 0.00001$) lowering of intraocular pressure one hour after parenteral administration of dichlorphenamide, when the rabbits were assured to be "responsive" by steroid administration.

EXPERIMENT 5.—As a final experiment, a group of eight rabbits was used to determine the effect of parenteral dichlorphenamide administration on aqueous bicarbonate concentration.‡ The plasma bicarbonate ion concentration was determined on all rabbits by Scholander's microtechnique [11] prior to the administration of dichlorphenamide, 100 mg. per kilogram given intraperitoneally. Five of the rabbits received the drug, while three served as controls. Control plasma bicarbonate levels were determined on all rabbits prior to the drug administration. After 1½ hours plasma and posterior chamber aqueous samples from all rabbits were

‡ The biochemical determinations were carried out by Dr. Everett Kinsey, of the Kresge Eye Institute of Wayne State University, Detroit.



Graph 3 (Experiment 4). — Intraocular tensions of rabbits receiving dichlorphenamide compared with those of control rabbits. All rabbits received fludrocortisone immediately after the —30-minute tensions were determined. Dichlorphenamide was administered parenterally immediately after the 0-minute tensions were determined. Each dot on the graph represents the average tonometer scale reading for one rabbit for five "runs" (10 determinations).

analyzed for bicarbonate ion concentration (Table 5). Although this is a small series, there is a significant drop in the bicarbonate ion concentration of the posterior chamber aqueous ($P \sim 0.00047$). A similar drop is noted in the plasma bicarbonate determinations. This would seem to parallel the similar effects of acetazolamide in lowering the rabbit aqueous bicarbonate ion concentration, shown by Becker.[12]

Summary and Conclusions

The importance of carefully controlled experimental studies with elimination of bias has been demonstrated in this series of experiments. In our preliminary experiment (Experiment 1) we were aware that all rabbits had received a drug which might well lower intraocular tension, and an apparently large hypotensive effect was found. Because of the large subjective element involved in rabbit tonometry, bias in taking the readings may well have accounted for all of this apparent effect. When this source of bias was eliminated in our subsequent experiments, no hypotensive effect of the drugs tested could be elicited under conditions which were similar except that smaller, younger rabbits were utilized in the subsequent experiments.

The New Zealand White rabbits used in Experiments 2 and 3, when fed a normal rabbit diet and given no special medications other than the drugs tested, demonstrated no significant lowering of intraocular tension after oral administration of acetazolamide,

TABLE 5 (EXPERIMENT 5).—*Data Showing the Effect of Parenteral Dichlorphenamide Administration on the Bicarbonate Ion Concentration of Plasma, and Posterior Chamber Aqueous of Rabbits Ninety Minutes After Drug Administration*

Rabbit	Drug Administered	Bicarbonate Ion Concentration, mM/Kg. of water		
		Plasma, Control	Plasma, 90 Min.	Posterior Chamber, 90 Min.
1	Dichlorphenamide	27.0	21.2	33.0
2	Dichlorphenamide	21.6	17.0	26.3
3	Dichlorphenamide	23.4	16.4	27.6
4	Dichlorphenamide	23.0	19.9	31.0
5	Dichlorphenamide	22.7	19.0	31.0
6	Control	26.7	26.0	41.8
7	Control	23.9	27.0	39.6
8	Control	21.6	27.4	41.8

dichlorphenamide, or chlorothiazide. This may correlate with Becker's report that certain rabbits are "pseudoresistant" to the hypotensive ocular effects of acetazolamide. Such rabbits may be "pseudoresistant" to other carbonic anhydrase inhibitors as well. However, the lack of hypotensive effect in these early experiments might also be due to the rapid metabolism of these drugs in the rabbit, with the hypotensive effect over before the post-treatment readings were made.

In experiment 4, parenteral administration of dichlorphenamide, with fludrocortisone to assure "responsive" rabbits, caused a significant decrease in the intraocular pressure of rabbits.

Dichlorphenamide was also found to cause a significant decrease in the bicarbonate ion concentration of the posterior chamber aqueous of rabbits even when they were not given fludrocortisone.

Department of Ophthalmology, Henry Ford Hospital (2).

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Cortical Blindness with Partial Recovery Following Acute Cerebral Anoxia from Cardiac Arrest

WILLIAM FLETCHER HOYT, M.D., San Francisco, and FRANK B. WALSH, M.D., Baltimore

Recently we have observed a patient who suffered cortical blindness as a result of cardiac arrest. Our studies on this patient have brought out some interesting features of this type of blindness and may serve to increase in some degree knowledge of the basic mechanisms underlying true cortical blindness as differentiated from blindness associated with more anterior involvement of the visual pathways. Cardiac arrest causes immediate catastrophic anoxia in the central nervous system. Anoxia of the cerebral cortex, regardless of the mechanism, forms the basis for all conditions leading to cortical blindness, with the exceptions of direct trauma and invasion by tumor. Through the opportunity to work with Dr. Richard Lindenberg * we have been better able to understand the visual symptomatology of cardiac arrest as exemplified by our patient. It is generally well known that severe hypoxia produces cortical changes particularly in the gray matter of the cerebrum and specifically of the visual, parietal, and motor cortex and basal ganglia. Furthermore, neuropathologists have recognized maximum damage in the cortical Lamina 3 and 4 of Brodmann. Thus, it might be anticipated that survivors of severe hypoxia, along with other neurological deficits, would have blindness. However, our patient with cardiac arrest recovered completely excepting for persistent blindness, and this specific feature is the subject of this paper.

Until recently, cardiac arrest invariably resulted in death. The introduction of thoracotomy and cardiac massage has provided recovery in some instances when performed without delay. In favorable cases recovery is complete, but in many cases evidences of widespread cerebral damage persist. Cortical blindness is only one of the residual defects, but we are not aware of it having been observed or reported as an isolated defect after cardiac arrest. With hypothermia as an adjunct to therapy, the residua of cerebral anoxia are being lessened.

Report of a Case

Cortical blindness following temporary cardiac arrest.

During the evening of Nov. 17, 1957, a 39-year-old Negro woman was brought to the accident room of The Johns Hopkins Hospital by ambulance. She had suffered multiple stab wounds of the right chest inflicted with an ice pick by a man with whom she had been living. She was conscious though somewhat dyspneic. She could see well and was oriented as to time and place.

Past history was significant only in that she had had pulmonary tuberculosis with cavitation in the left chest involving primarily the left apex.

Pneumothorax was suspected, and an x-ray was taken with a portable x-ray unit in the accident room. This x-ray revealed pneumothorax in the right chest cavity. Aminophylline had been given to increase her respiratory exchange just before this x-ray examination was made.

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Reported from the Wilmer Institute of The Johns Hopkins Hospital; Heed Foundation Fellow (Dr. Hoyt).

* Director of The Central Anatomic Laboratory of The Maryland State Department of Mental Hygiene and the Division of Legal Medicine, University of Maryland School of Medicine.

Cardiac Arrest, Emergency Thoracotomy Performed.—During the time the x-ray examination was being performed the patient suddenly had acute respiratory distress and became unconscious. It was noted immediately that her heart had stopped beating. Within a period of one to two minutes (reports vary in her history) her left chest was opened and manual massage of her heart was begun. Within a period of three to five minutes normal heart beat and blood pressure were restored. The pneumothorax was controlled with catheters placed in both chest cavities.

Hypothermia Begun.—To combat the inevitable effects of acute cerebral hypoxia (brain swelling) the patient was placed in hypothermia within one to two hours after thoracotomy. Within two to four hours after cardiac arrest her body temperature was lowered to 88 F. She remained in critical condition in deep coma. The pupils were dilated and fixed and did not respond to light.

Hypothermia Maintained for Three Days: Coma Thirty-Six to Forty-Nine Hours.—The patient was held in a state of hypothermia for a period of three days, and her body temperature remained at a level between 88 and 92 F. Blood pressure was maintained at about 100-105/75. Twenty-four hours after the onset of the cardiac arrest there was doubt whether or not she would live. The next day she could be aroused with loud verbal stimuli and with a loud hand clap. During the afternoon of that day she could answer questions by shaking her head and was able to talk, though indistinctly, uttering such phrases as "Oh doctor," "What happened to me?" and "Where am I?" Neurological examination revealed bilateral extensor rigidity and bilateral "down going" toes. The next day the patient's condition was approximately the same; however, a note was made that her pupils responded briskly to light. Hypothermia had been discontinued. Within 12 hours she was able to talk readily and her comprehension was good.

Phase of Recovery.—By Nov. 21 the prognosis seemed much improved, for her blood pressure was stabilized at 110/80 and she could talk distinctly and rationally. She could move her extremities on command. She could remember all that had transpired up to the time she arrived in the accident room. Extensor rigidity was no longer present, and reflexes were equal and active. It was remarked at this time that the cranial nerves were "intact."

Cortical Blindness Discovered Nine Days After Cardiac Arrest.—On Nov. 26 her condition was sufficiently stable to warrant moving her to a general hospital ward. During this move, while her bed was being pushed through crowded hospital corridors and onto elevators, the patient herself realized that these parts of the hospital must have been illuminated; however, she was unable to see the people whose voices she heard all around her. Previous to this she had assumed that she had been in a darkened room where a very dim night light was burning. Though she wondered at times how the nurses could do their work in such dim light, it had not occurred to her that she was blind. At this time neurological examination revealed that her reflexes and general body sensations were intact, and she had no positive cerebellar signs. She was oriented and responded accurately to command. Her speech was somewhat childish, as was her behavior. She would often repeat phrases and would occasionally reverse words in their normal order in sentences. She was unable to do serial "7's" and was unable to multiply or divide simple numbers. She talked slowly. According to her daughter, her behavior was not normal.

The patient stated she was able to see a "grayish hazy light" around her, but she was unable to recognize a small hand light in any part of the visual field of either eye. She could not perceive hand motions. Her pupillary reactions and optic fundi were entirely normal. She was able to move her eyes in all directions on command. Optico-

kinetic nystagmus was absent. She had no visual blink reflex or accommodation-convergence reflex, nor did she admit to any visual hallucinations. At this time classical cortical blindness was recognized.

Remainder of Course in Hospital.—The patient continued to improve, her speech difficulty improved, and she was able to walk with assistance in the ward. Her blindness remained profound, but she claimed she could see vague grayish light. On Dec. 13, twenty-three days after cardiac arrest, she was discharged to her home, and just prior to this she reported that she could vaguely see motions of her right hand in her right field of vision. This finding was not confirmed.

Subsequent Course at Home: Slow Return of Vision.—She seemed to do well and was far from helpless. Her changes in behavior and her speech difficulties cleared completely. Within two weeks of her arrival at home she became aware of true light perception. She noted that it made a difference whether her bedroom light was on or off. In late December she thought she could see light in doorways and vague form. On one occasion she correctly identified color. At Christmas time she first became aware of motion. This occurred as her small nephew was pushing a toy truck back and forth on the floor below her. From then on she became convinced that her vision was slowly returning. Although she could now see her hand moving before her eyes, she could not see her image in the mirror. After a few days she could identify colors and gross form without error.

Eye Examination on Jan. 14, 1958 (Two Months After Cardiac Arrest).—The patient was seen at the Wilmer Institute for the first time since her discharge one month previously. Her pupillary reactions were normal, as were her optic fundi. She was able to fix on large objects held directly in front of her. She could see hand motions throughout her entire right visual field; however, in the left field she was completely blind except for a temporal crescent in which she could see only hand motions. Objects which were not in motion were not perceived in any part of her field except in the upper right quadrant. She could fix on a large (4×4 in.) white object on the perimeter. Her color discrimination, at least with crude testing, was without error, although she could not see well centrally and could not count fingers accurately even at 1 ft. (Fig. 1).

Examination of her visual fields was repeated one week later, and marked improvement was again noted. Her right field was now sensitive to much smaller test objects; even a 5 mm. object was seen in the right upper field at 1 meter. The temporal crescent on the left was also sensitive to 6/330 white test objects. The dissociation in perception between moving and stationary test objects was evident in the right lower quadrant. Her macula was now split directly through the middle. Her visual acuity centrally was still very poor, and she could count fingers only at 2 ft. (Fig. 2).

Subsequent visual field examinations showed no pronounced improvement.

Visual Spatial Disorientation Also Present.—The patient's fixation was excellent. However, she was agnostic for the left half of her central field and would not search or compensate for her hemianopsia. When attempting to count fingers she would consistently see only the fingers on her right and would not shift fixation to correct for repeated errors. She could locate single objects in space but could not count multiple objects presented in her seeing field. She was not agnostic for form (she could name and describe simple objects such as triangles, squares, and circles). Her topographical memory was fair, but she often said right when she meant left. She and her daughter both reported that she would often confuse right and left turns when walking in the street. During examination when she arose from a chair she would often turn in the wrong direction in order to leave the room. She had this difficulty at home. She had no apraxia for

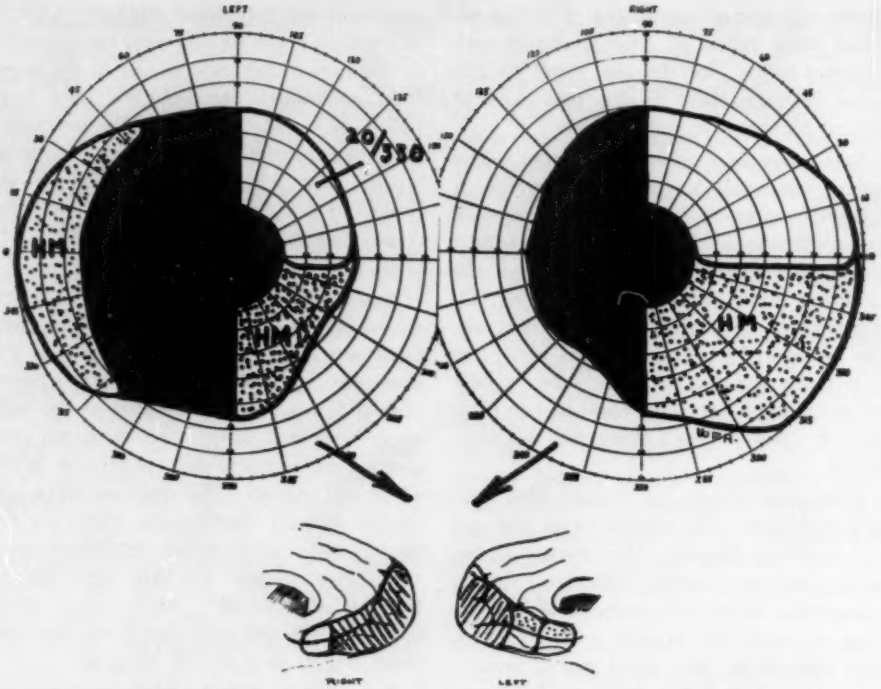
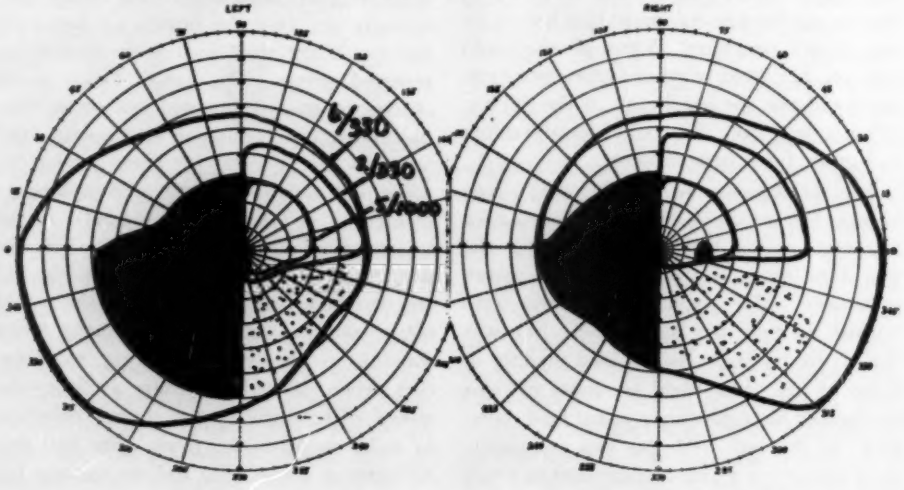


Fig. 1.—Visual fields show return of perception of hand motions (H. M.) in the left temporal crescent and in the right lower field. Perception of a 20/330 white test object was present in the right upper field. The central area was blind, as was the left homonymous field. The schematic diagram below indicates the approximate distribution of damage to the visual cortex inferred from the visual field examination.

Fig. 2.—Subsequent visual fields, showing recovery especially in the right field. The dots indicate the homonymous areas where moving test objects only could be perceived.



dressing (she never made errors putting on her coat or sweater). She had no right-left confusion on her own body, though she stated that sometimes she "only seemed to have a right side." She made no errors in speech and had good memory for events. When attempting to divide a line in half or place a center in a circle she consistently made an error to the right side.

Impression.—Cortical blindness with partial recovery associated with mild spatial disorientation following severe cerebral hypoxia due to cardiac arrest.

1. Features of Cortical Blindness Evidenced in this Case

The failure of recognition of blindness by the patient (Anton's syndrome) and by her examiners exemplifies a common feature of such cases. The severity of the process and the slow return of consciousness could explain the early unawareness of our patient, but the long-continued early unawareness is due to agnosia for the blindness (anosognosia). The diagnosis was overlooked until the patient herself drew attention to it because she behaved as if she could see and because the pupillary reactions to light remained and the optic fundi were normal. The agnosia may be mild or profound, depending on the degree of involvement of the visual association areas and of the subcortical white matter. In a quiet hospital room even when the agnosia is mild the patient may be unimpressed by inability to see and may assume (as our patient did) that such inability is due to the "poor" lighting.

Recovery from cortical blindness may be slow and may not start for a period of weeks after onset. Furthermore, the ultimate degree of recovery may not be complete for months (Bergman). Patients with true cortical blindness of sudden onset who are otherwise well usually regain part or all of their sight. As exemplified by our patient, residual field defects plus persistent agnosia including disability as regards topographical memory and disorientation in space constitutes a severe visual disability. The affected person may be "blinder than the blind."

Riddoch discussed perception of motion as an early sign of returning vision. A large stationary object may be completely overlooked while a small test object in constant motion will be immediately recognized. This cannot be explained simply by saying that a moving target stimulates more receptors and, therefore, can be more readily perceived. Riddoch's observation held true in our patient. We have observed such a dissociation in cases of traumatic cortical blindness.

From the visual fields in particular, we have drawn the following conclusions as regards the case here reported. The return of vision started peripherally and finally arrived at fixation (on the right). This indicated that principal damage occurred at the posterior pole. On the left the temporal crescent returned followed by return of a small portion of the peripheral field on this side. This indicated return of function in the contralateral anterior part of the calcarine cortex. In our patient the return of the peripheral visual perception did not imply the return of function of much of the visual area—quite the contrary.

We may deduce that the right calcarine cortex in our patient and the right posterior poles were very severely damaged, that the left occipital lobe was less severely affected than the right, and that the posterior pole was the most affected.

Important Feature as Regards Return of Visual Field.—In a majority of cases of cortical blindness and bilateral homonymous hemianopsia return of vision commences centrally (Symonds and MacKenzie, 1957). In our patient return of vision commenced peripherally. It is obvious that return of vision is dependent upon the severity of the involvement of specific parts of the visual cortex. The more severe involvement of the posterior portions of the visual cortex (as observed in our patient who suffered severe cerebral hypoxia) will be ampli-

fied further in discussion of specific effects of hypoxia involving the visual cortex.

2. The Role of Hypoxia

Hypoxia is oxygen lack at the cellular level. Hypoxia of cortical cells may result from any mechanism which interferes with the oxygenation of hemoglobin, oxygen transport, or oxygen utilization at the cellular level (Courville). Any acute respiratory difficulty may lead to cerebral hypoxia. Severe anemia with a deficiency of oxygen-transporting cells (RBC) causes cerebral cortical hypoxia. Carbon monoxide or nitrous oxide in high concentration loads the red blood cells with a substance which displaces oxygen, and, therefore, again insufficient oxygen arrives at the cellular level and hypoxia of the cerebral cortex results. Some substances may interfere with the cellular utilization of oxygen, but this, too, is in essence hypoxia.

As illustrated by our patient, an event par excellence leading to profound hypoxia is cardiac arrest. The entire transport system of oxygen is stopped (stagnant anoxia). Our patient suffered arrest lasting three to five minutes, which is within the critical period established by Weinberger (working with cats) and Kabat and Dennis (working with dogs). Weinberger found that permanent changes in the cortical cells followed hypoxia lasting longer than 3 minutes 10 seconds and that beyond 7 minutes death occurred. He showed that the visual areas, motor areas, and basal ganglia are particularly susceptible to damage by hypoxia and that the subcortical white matter and particularly the brain stem and spinal cord are relatively resistant to hypoxia. Furthermore, certain layers of cortex (Layers 3 and 4 of Brodmann) are particularly sensitive to oxygen insufficiency. Since these layers are best developed in the calcarine cortex, disturbances of vision are to be anticipated in generalized hypoxia, according to Courville. The recovery of our patient except as regards visual functions exemplifies a rare occurrence if the general experience has been parallel to that reported by Turk, who recorded after 40 similar procedures for cardiac arrest no occurrence such as we have described here.

The Changes in the Cortex Resulting From Hypoxia.—Courville (1958) has reviewed this subject, and he and others have stressed the importance of the correlation of hypoxia with a great number of thus far poorly understood neuropathologic changes. When the cortex is deprived of oxygen, almost immediate congestion occurs. The white matter is more resistant to hypoxia and congestion than the gray matter. Hypoxic effects occur rapidly in the basal ganglia and in the cerebellum. For years laminar cortical necrosis (selective necrosis of certain intermediate layers of the cerebral cortex) has been recognized, and it was described as early as 1858 by Mitchell, who considered it to be of inflammatory origin. Sometime later Fischer described it as "spongiöse Rindenschwund" and assumed it was of circulatory origin. Laminar cortical necrosis is the presently used term for this type of cortical change. The change seems to be dependent on the laminar cellular architecture of the cortex, and according to most authors this necrosis occurs in Lamina 3 of Brodmann but may extend to Lamina 4, 5, and even 6. Such cortical degeneration was first noted in dementia paralytica and later in many types of cortical atrophy, in some cases of idiocy, in congenital microgyria, and even in epilepsy. During the 1920's much work was devoted to this subject and the condition was described in acute as well as in chronic conditions. Bodechtel (1928) described this laminar cortical change in patients who died as a result of cardiac arrest associated with lumbar anesthesia. It had been described in asphyxia on a mechanical basis. The same phenomenon was described in fatal cases of morphine poisoning and in lead poisoning and in patients dying of overdosage of barbiturates. It is understandable why a "toxic" theory developed to explain laminar necrosis. However, it was always baffling that so many different agents and accidents

caused an indistinguishable change in the brain. Gradually the evidence pointed to impairment of cortical circulation as a common denominator. These lesions were most commonly found in cerebral embolism, arteriosclerosis, and syphilitic vascular disease but were also described in profound drops of blood pressure following cardiac arrest and shock, in asphyxia due to carbon monoxide poisoning, in choking, and in cases of pilots dying anoxic deaths due to failure of oxygen systems at high altitudes. (Hoff, Grenell, and Fulton). Finally it became apparent to such workers as Courville that there was an even more basic common denominator for all this, namely, cerebral cortical oxygen want or hypoxia at a cellular level.

In the cortex there is a lamellar distribution of capillary nets originating at the surface of the cortex; these are most dense in the deeper cortical layers, particularly in Lamina 3. Apparently the cortical cells at this level need a greater blood supply. When the oxygen supply is slowed or stopped and hypoxia results, these cells suffer first. As a response to hypoxia the cortical cells swell. Increased permeability of the capillary walls accounts for fluid pouring out into the surrounding tissue. Small petechial hemorrhages occur in this phase. Swelling advances into neighboring layers of the cortex and circulation is further embarrassed. Unrelieved hypoxia over a longer period leads to cortical necrosis.

It was noted early that laminar cortical necrosis first occurred in certain areas of the cortex. These areas were described regularly as the visual areas, the premotor areas, and, sometimes, the parietal areas. It was further postulated that certain cortical areas were target areas of hypoxic insults. Courville stated that these areas were selectively sensitive to hypoxia because of their seemingly greater oxygen demand. Lindenberg (1957) has explained this paradox simply on the basis of border zones of cerebral circulation. He believes that it is unnecessary to postulate that one area of the cortex needs more oxygen than another. He believes that the cortex at the terminal areas of the three main cerebral arteries suffers earlier and more than cortex situated elsewhere. The border zones between the anterior and the middle cerebral arteries are two sagittally oriented bands which extend from the premotor area of the frontal lobe backward parasagittally almost to the occipital pole. The border zones between the middle and the posterior cerebral artery extend along the lateral and superior edges of the occipital lobe to the occipital poles. Lindenberg states further that this border-zone necrosis almost specifically implies temporary cardiac failure. This pattern of necrosis is the lesion of cardiac arrest in the brain. His concept seems to explain

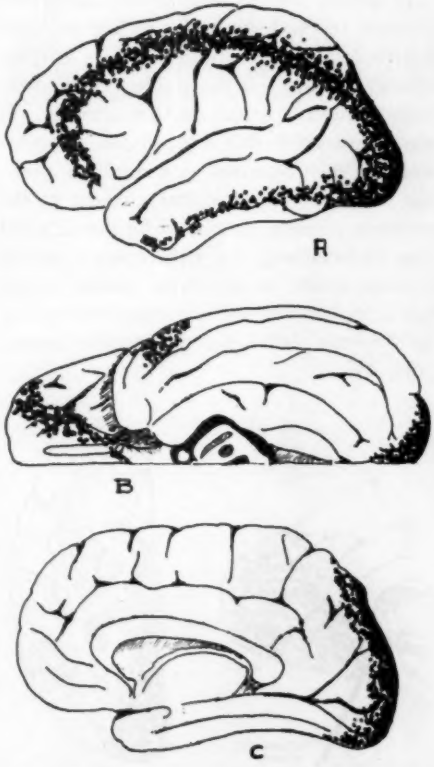


Fig. 3.—Diagrammatic representation of the border zones of cerebral circulation. The stippled area represents the border zones. Note that the occipital pole is a border zone of all three major arteries of the cerebrum. Hypoxia following cardiac arrest occurs principally in these areas. (See text.)

reasonably the selective involvement of various areas of the cortex, especially of the occipital poles (Fig. 3).

It was noteworthy that other evidences of cortical damage (motor cortex, cerebellum, and basal ganglia) did not develop in our patient, considering the severity of the involvement of the visual cortex. Convulsions were not a feature as is so common in cases of generalized cerebral anoxia (Courville, 1936; Ford, Walsh, and Jarvis, 1937; Reese, 1954). We believe that there are two main reasons why our patient exhibited cortical blindness and failed to show signs indicating more extensive cortical damage. These factors are hypothermia and transtentorial shift.

If we are correct in believing that hypothermia relieved cerebral swelling in some degree and favorably influenced the cortical damage, we are left the problem of the profound selective visual cortical damage. It seems reasonable that some degree of transtentorial shift occurred as a result of swelling and that through embarrassment of the posterior cerebral circulation by the tentorial edge (Lindenberg 1955) there was a second hypoxic insult to the visual cortex, which had already been severely compromised by the hypoxia following the cardiac arrest. (Fig. 4).

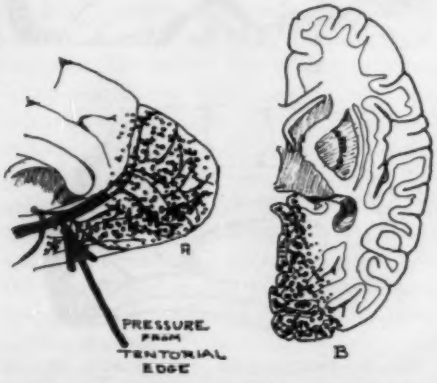


Fig. 4.—The diagram indicates (arrow) the site of obstruction of the branches of the posterior cerebral artery subsequent to transtentorial herniation. The stippled area indicates the distribution of the resulting cortical hypoxia.

Summary

A case of cortical blindness resulting from cardiac arrest and resultant cerebral hypoxia has been described. This case illustrates true cortical blindness as differentiated from blindness arising from more extensive le- the eponym bilateral homonymous hemisions such as are frequently described under anopsia.

Interesting features of cortical involvement resulting from hypoxia are recounted. Attention is directed to basic work which shows that hypoxia influences particularly Laminae 3 and 4 of the cortex and that the visual cortex is particularly susceptible (also the motor cortex, basal ganglia, and cerebellum).

In our case profound involvement of the visual cortex without evidence of involvement of other cortical areas seemed to require explanation. We suggest that in this patient hypothermia may have avoided some of the cerebral damage which characterizes such cases. However, particular vulnerability of the posterior pole of the brain to acute anoxia plus some degree of transtentorial herniation (with resultant embarrassment of the blood supply to the visual cortex) well may explain cortical blindness in our patient.

Department of Ophthalmology, University of California Medical Center.

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Hemangiopericytoma

EDMUND B. SPAETH, M.D., and ANTONIO VALDES-DAPENA, M.D., Philadelphia

Among the 26 cases of primary orbital tumors studied in the pathology department of the Graduate Hospital in the last nine years there was a predominance of lymphoid tissue tumors (7 cases) and neurogenic tumors (5 cases). There were only three vascular tumors, and one of these was the case under discussion; the other two were hemangiomas, which Reese[1] found to be the commonest in his extensive series of orbital neoplasms.

This case now presented illustrates the seriousness of a condition ordinarily considered to be of relatively low malignancy. The patient, a man aged 36, was referred on Dec. 8, 1951, by Dr. R. E. M., of New York, with a tentative diagnosis of retrobulbar hemangioma, with exophthalmos, with swelling of the upper lid, and with accompanying ptosis. The condition was of 18 to 24 months' duration and was slow in onset.

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The Graduate Hospital, The Graduate School of Medicine, University of Pennsylvania, Department of Ophthalmology (Dr. Spaeth) and Department of Pathology (Dr. Valdes-Dapena).

Fig. 1.—Close-up of involved eye.

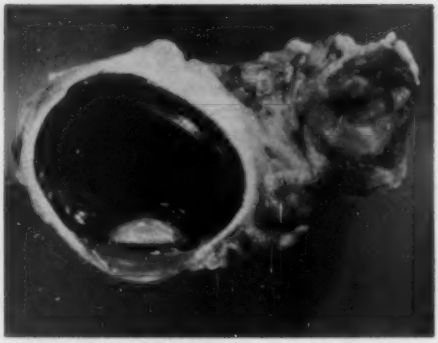

Fig. 2.—Enucleated eye, equatorial section, showing extrabulbar tumor.

A manifest, easily palpated lesion was present in the upper portion of the orbit behind the upper lid, displacing the lid forward, displacing the eyeball downward, and everting the upper lid and the tarsal plate. Visual acuity was 6/22. There was no fundus pathology.

On Dec. 18, 1951, an uneventful orbitotomy was done, the incision being below the eyebrow, with an uneventful removal of a large encapsulated blood vessel tumor which, at the operating table, seemed to be a hemangioma.

The tissue was sent to the laboratory with that diagnosis. The report which was returned from the laboratory was that of a poorly differentiated vascular tumor, hemangiopericytoma, described, at the time, as follows: "Sections show a very cellular tumor. It is not an epithelial type of growth. The predominant type of cell is one with a very indistinct cell border and an oval nucleus which is rather smooth in appearance and is reminiscent of those found in poorly differentiated vascular tumors. Occasional vascular spaces are formed. Some of these are large and in that case the neoplastic nuclei seem separated from the endothelium

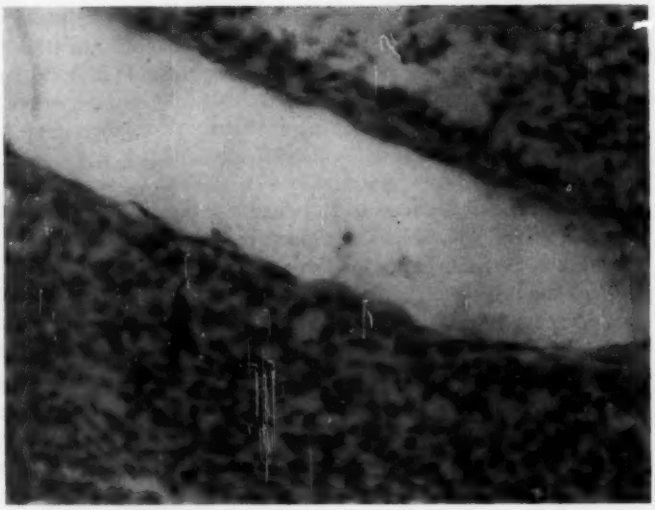

Fig. 3. — Photomicrograph of first operative specimen. Tumor cells around vessel can be distinguished from flat endothelial cells lining it.

by a thin rim of amorphous substance. Well defined capillary formation is very scarce. There are accumulations of pink staining amorphous substance which may be related to intercellular capillary cement. Miotic figures are seen here and there. It is our impression that this is a poorly differentiated vascular tumor of low grade malignancy. Because of the lack of tendency to form capillaries we attribute the growth principally to proliferation of perivascular elements."

The patient's postoperative convalescence was uneventful, and he returned to his home in Connecticut on Dec. 29, 1951. At that time he was returned to an ophthalmologist, Dr. R. F., of New Haven, for continued postoperative observation.

On April 27, 1953, the patient returned to the Graduate Hospital with a recurrence in the orbit and with exophthalmos which seemed to be almost as extensive as that seen at the time of the first surgery. On April 30, 1953, a complete exenteration of the orbit was done, including all tissues of the upper and the lower lids and all the soft tissues of the orbit, including the periosteum of the bones of the orbit.

The microscopic report had, at this time, three interesting aspects: first, "Our impression, grossly, is that this has been a well circumscribed growth"; second, "the mass is covered by smooth membrane with a bluish color and over most of its surface this mass is covered by this thin membrane"; third, "recurrent, encapsulated hemangiocytoma is the diagnosis."

On Nov. 13, 1953, the note on the follow-up study was that "the patient has a completely healed socket, to return in six months for a socket reconstruction." On March 10, 1955, almost two years after the exenteration, the patient returned for the socket reconstruction. This was an uneventful procedure. On July 8, 1955, the office note was "full recovery, the orbit has healed entirely; to return in the fall."

On Nov. 1, 1955, the patient's wife telephoned that "bleeding blisters" were appearing in the depths of the patient's socket. The patient was not wearing a prosthesis at this time. He had not as yet decided as to the desirability (on his part) of further plastic surgery so that a prosthesis could be worn. The patient's wife was advised to have the patient return immediately for further observation. The patient was readmitted to the hospital on Nov. 7, 1955.

The surgery, on Nov. 8, 1955, was the resection of two areas of recurrence. The microscopic diagnosis of Nov. 8, 1955, had

one significant comment: "The sections show a nest of tumor cells rather deep under the surface epithelium." This surface epithelium consisted of the graft. At this time the patient was given slightly more than 4000 r of x-ray therapy, delivered within a three weeks' period. On Feb. 5, 1956, the patient returned to the office for reexamination. The situation seemed to be wholly satisfactory, and work was started on a plastic prosthesis for the patient. This was completed and fitted to the patient on March 31, 1956. On Oct. 27, 1956, the patient was seen in the office and a report was sent to his physician that recovery again seemed to be satisfactory.

On Feb. 2, 1957, the patient returned to the office with a definite recurrence in the orbit, a pulsating mass described by the patient, at the time, as "a small knot or lump." The patient had neuralgia-like pains on the side of his face and into the forehead.

On Feb. 7, 1957, further extensive exenteration of the orbit was done, with removal, at this time, of the roof of the orbit, the medial wall of the orbit, and the posterior wall of the orbit, exposing a mass adherent to the periosteum of the lateral wall of the orbit and to the dura in the anterior fossa. While no x-ray studies had been made, the bone, as well as the periosteum, of the orbit showed no gross pathology whatsoever. On Feb. 12, 1957, the postoperative packing was removed and 16 radon seeds were implanted into the tissues at that area. On Feb. 27 the patient was discharged from the hospital for observation by his home physician and he was instructed to return early in March. On March 2 he returned to the office, showing four new recurrences in the operative area. The largest was about the size of an almond; the smallest, the size of a pea. At this time there was considerable discussion in the department of ophthalmology as to whether γ-radiation from a Co^{60} source or radium should be used. Consultation with the isotope unit at Temple University Medical School resulted in the decision that radium capsules should be used rather than the cobalt radiation. The microscopic reports for Feb. 7 and April 2 continued to be those of hemangiopericytoma.

On April 11, 1957, radium, 70 mg., was implanted into the orbit for an estimated dosage of 5000 mg-hr. This dosage was divided into 10 capsules, these being placed so that the entire area of the operation would be evenly treated. The patient was discharged from the hospital on April 13, and he was seen in the office on June 8. Both the patient and the ophthalmologist following the case reported that in the interval several of the radon seeds had spontaneously extruded. The orbit was clean, without signs of any recurrence.

On Aug. 9 the patient, when last seen, showed no signs of recurrences. Packing was entirely discontinued, and the patient was advised to return in six weeks.

One month later the referring physician reported by telephone, "recurrences are appearing in the area formerly occupied by the orbit, with headaches, dizziness, and other signs of certain intracranial extension." It was thought that further surgery should not be carried out and that additional irradiation therapy would also be hopeless. The remaining eye showed exophthalmos and was completely fixed in the orbit. The recurrences were, apparently, in the middle fossa of the cranial cavity, over both sides of the cranial base.

It is to be noted that hemangiopericytoma was not described until 1942, and then by Murray and Stout.[2] Except for one case, no other author had made a contribution to the literature of this tumor when Stout[3] reported 25 new cases in 1949. Since that time, case reports on the subject have become commoner. When the first slides of this case were studied histologically, the diagnosis was offered with some mental reservations. The slides were submitted to Dr. Stout, who confirmed the diagnosis. Successive reports made on the recurrences made reference to a certain loss of differentiation as represented by a decrease in

number of well-defined blood spaces. Nevertheless, the visual impression gained from microscopic study was never that of an unbridled malignancy. The course of the disease in this case is typical of many soft tissue tumors. These are inclined to be locally malignant rather than to spread by blood stream or lymphatics.

In considering the histology of this lesion, hemangiopericytoma, the "Atlas of Pathology, U. S. Naval Medical School," [4] states that this is a neoplasm with numerous endothelium-lined spaces containing red blood cells and surrounded by a meshwork of reticulum cells and fibroblasts. These elaborate a collagenous matrix which may undergo hyalinization. Nuclear pleomorphism indicates a fairly high degree of malignancy. The capillary spaces are lined by endothelial cells which bulge into their lumens. The perivascular tumor cells outside the capillaries are without definite arrangement. Stout believes that the pericyte is the cell of origin of these neoplasms and that in its differentiation it may approach on the one hand a smooth muscle cell and on the other hand a glomus epithelioid cell. These basic cells are not endothelial cells. Anderson,[5] in discussing this neoplasm, states rather casually, "these lesions are generally benign, but one deeply infiltrating example and one with a metastasis have been described." Reese,[1] in his textbook "Tumors of the Eye," states, "all these tumors may be malignant, and any one of this group is sometimes called an angiosarcoma."

One must wonder whether the surgery as first done was too timidly carried out. Certainly the subsequent surgery could not have been more extensive—that is, the complete removal of the orbital contents, the contiguous tissues, and finally the orbit. A second point of interest is the complete irradiation-resistance of this neoplasm. A third point, and one of the greatest significance, is the decision as to what therapy is to be carried out in the treatment of this rare neoplasm.

The feasibility of a wide local resection must be the keystone of the prognosis. In the orbit one is dealing with a rigid compartment that limits the extent of surgical resection. One must theorize that small satellite growths, created by direct extension from the main tumor mass, are able to escape the early operative procedures and remain, probably in minute bony and soft tissue crevices, until their increase in size brings them again into view. From the time of the initial lesion it is a question of attacking not one but a number of centers of growth throughout the periphery of the original tumor site, some originally present, others perhaps related to the operative procedures.

While hemangiopericytomas are to be considered as a group of tumors of low-grade malignancy, this is a conditional evaluation. If the location is such that uninhibitedly wide excision is impossible or not to be lightly undertaken, the local aggressiveness of the neoplasm throws a different light on the prognosis. This is illustrated by the present case.

Conclusion

This single case presentation, with relevant comments about a rare neoplasm, seems to offer some significant information which may be of assistance to others.

1930 Chestnut St. (3).

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The Experimental Production of Papilledema

WILLIAM B. GLEW, M.D.; THOMAS P. KEARNS, M.D.; C. WILBUR RUCKER, M.D., and HIRAM E. ESSEX, Ph.D., Rochester, Minn.

Few problems in ophthalmology have provoked more speculation than the pathogenesis of papilledema. Though extensive investigations have been carried out over a period of almost a hundred years, many gaps remain in our knowledge of this subject. Most of the existing information about papilledema has been provided by clinical and pathologic studies rather than by experimental investigation. These studies and the various mechanisms of the pathogenesis of papilledema hypothesized by their authors have been reviewed adequately by Brégeat,[1] Duke-Elder,[2] and Walsh.[3]

The majority of published experimental studies of papilledema fall into three categories: (1) attempts to simulate expanding intracranial lesions, (2) elevations of intracranial pressure for short periods, and (3) the production of internal hydrocephalus. Though reports of many of these experiments have asserted the production of papilledema in animals, the methods employed have not yielded consistently reproducible results.

Unfortunately, reports of the production of papilledema were documented in most cases only by histologic sections of the optic disc. As pointed out by Wolff and Davies,[4] these sections are difficult to evaluate because of changes produced in the optic nerve simply by histologic fixation. Photographs of the fundi were not used for documenting experimentally produced papilledema in the literature examined.

In man, papilledema rarely appears until more than 12 hours after the appearance of symptoms of intracranial disease; but of the reviewed experiments dealing with the relationship of intracranial pressure to papilledema in which pressures were actually measured, none had lasted longer than 12 hours.

The objective of this investigation was to find a method of producing papilledema in animals analogous to the bilateral papilledema associated with intracranial disease in man.

Preliminary Studies

Attempts to produce papilledema in dogs by use of the methods of Cushing and Bordley[5] and of Parker,[6] which employed the insertion of sponges between the skull and the dura and also the production of ocular hypotony, were unsuccessful in 10 animals. Further attempts were made to produce papilledema in three dogs by means of a technique used by Schurr and coworkers[7] in which hydrocephalus was produced by injections of iophendylate (Pantopaque) into the cisterna magna. Hyperemia of the disc and a small splinter hemorrhage adjacent to the disc developed in one dog. Papilledema did not develop in any of the three. At necropsy, six weeks to three months later, the ventricles of all three dogs showed marked dilatation. The negative results of these attempts to produce papilledema in dogs are in accord with the findings in the study of hydrocephalus made by Ingraham and associates.[8]

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Abridgment of thesis submitted by Dr. Glew to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Ophthalmology.

Assistant to the Staff (Dr. Glew), Section of Ophthalmology (Drs. Kearns and Rucker), and Section of Physiology (Dr. Essex), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

They, too, observed hyperemia of the disc and an occasional hemorrhage, but they found no papilledema in any of their animals.

In man, papilledema is associated with dilatation of the third ventricle in a high percentage of cases. Yet papilledema was not observed in dogs with third ventricular dilatation in the study by Ingraham and associates or in the present study. For some unknown reason, it appears that papilledema occurs less readily in dogs than in man. In view of the failure to produce papilledema in dogs, further efforts were applied to the Macaca mulatta (rhesus) monkey.

The method which proved to be successful in the production of papilledema in monkeys was the gradual inflation of an intracranial balloon. This method had been used by Merz [9] in 1900 in unsuccessful attempts to produce papilledema in the rabbit and dog, by Simmons [10] in 1947 in attempts to produce cerebral edema in the dog, and by Stellar and Cooper [11] in 1955 to simulate tumors of the cerebellopontine angle in dogs. The method evolved in this study is a slightly modified combination of the techniques employed by these several investigators. It was found that when placed in the subdural space above the tentorium the balloon produced less morbidity and mortality than when it was placed in the posterior fossa or in the substance of the brain itself.

Materials, Methods, and Procedures

A number of experiments were performed on a total of six monkeys.

Operative Procedure.—Each animal was anesthetized with approximately 25 mg. of thiopental sodium per kilogram of body weight. Under routine surgical asepsis a parasagittal incision was made approximately 3 cm. to the right or left of the midline. The temporalis muscle and periosteum were incised along this line and retracted to either side. An opening 1.5 cm. in diameter was then trephined in the skull. The dura was incised. A thin-walled rubber balloon of 30 cc. capacity or less into which a polyethylene or polyvinyl catheter was tied (Fig. 1) was collapsed and inserted into the subdural space over the brain. The dura was closed with 00000 nonabsorbable surgical (silk) sutures around the catheter. A hole was then drilled into the trephined disc of bone, and the catheter was drawn through this hole and through the center of a plastic cylinder, and the disc of bone was fastened to the surrounding skull with three silver-wire sutures which were passed through small holes drilled in the disc and adjacent skull table. The plastic cylinder was fastened to the skull with three wood screws and dental acrylic plastic, which hardened around the screws and the cylinder. Iodopyracet (Diodrast) then was inserted through the tube into the balloon. The tube was plugged and coiled over the top of the cylinder, and a plastic cover was screwed down over the top of the cylinder.

Fig. 1.—Balloon tied around polyvinyl tubing which passes through hole in plastic cylinder and coils in cap of cylinder.

Skull Roentgenograms.—The radiopaque iodopyracet allowed the size, shape, and location of the balloon to be determined by postoperative roentgenograms.

Fundus Photography.—With the animal anesthetized and the pupils widely dilated by 1% atropine, the fundi were photographed.

Measurement of Pressure in the Balloon.

At intervals of two to five days the animal was anesthetized and placed on a table with the prepared side of the skull uppermost. The plastic cap was removed,

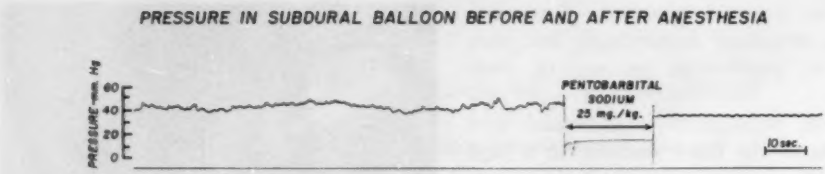

Fig. 2.—Recording of pressure from subdural balloon, demonstrating relative stability of pressure in the anesthetized animal.

and the tube was connected to a strain gauge. The pressure in the balloon was then recorded and calibrated with a mercury manometer, the ambient atmospheric pressure being taken as zero. Pressures recorded from the anesthetized animal were very stable (Fig. 2), as the variations due to the transmission of the arterial pulse and to the variations in venous pressure with respirations usually were not greater than 3 mm. Hg. The approximate mean of these minor variations of pressure was the pressure recorded in the description of the experiment. Prior to each pressure recording, at least 24 hours had elapsed after insertion of the previous increment of fluid into the balloon. By taking simultaneous recordings of pressure in the balloon and in the cisterna magna in three experiments it was found that the pressure in the balloon followed closely the pressure of the cerebrospinal fluid in the cisterna magna. The rate of inflation of the balloons and the pressures measured from the balloons were similar in all of the animals.

Experiments

Animal 1.—*Left Lobe.*—In one monkey, which weighed 2.5 kg., a balloon of 20 cc. capacity was inserted over the lateral aspect of the left temporal lobe. After the animal's uneventful recovery and the usual preparations, ophthalmoscopic examination revealed that the optic discs were still flat, with sharp margins. At operation and at intervals of two to four days thereafter small increments of iodopyracet were inserted into the balloon. Eight days after placement of the balloon the nerve fiber layer in the peripapillary region of each eye appeared more gray than the surrounding retina and the disc margins were not so distinct as had been noted previously. On the 10th day there was a slight but definite elevation of the retina in the peripapillary area, greater on the left side than on the right. The disc margins were blurred, and small dilated venules were visible at the edges of the discs and on them. Some of the smaller vessels were covered in part of their course by edematous retina. On the 12th day more fluid was inserted, making a total of 3.75 cc. of iodopyracet in the balloon. On the 16th day fundus photographs were taken (Fig. 3*a* and *b*). Superficial hemorrhages were observed on the left disc, which was elevated 1 D. The right disc was elevated less

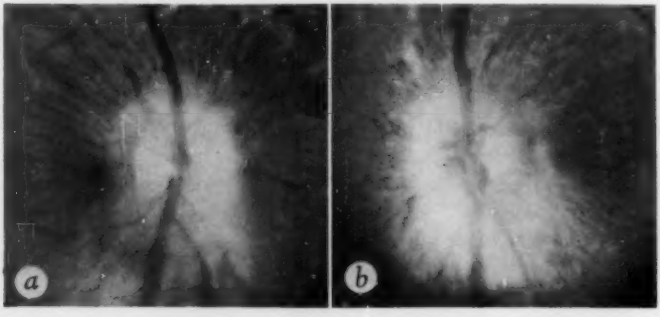

Fig. 3.—Fundus photographs demonstrating papilledema in the right (*a*) and left (*b*) eyes of a monkey.

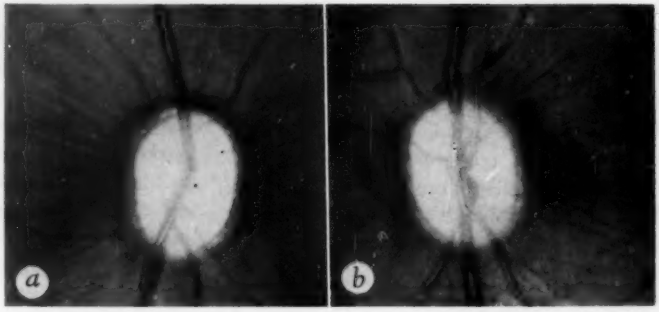

Fig. 4.—Fundus photographs showing the same optic discs as in Figure 3, right (*a*) and left (*b*), after subsidence of papilledema.

than 1 D. On the 23d day the hemorrhages and edema appeared to be resolving. On the 27th day the tube was cut and the fluid was allowed to escape from the balloon. Thirty-four days postoperatively the fundi were normal except for slight residual grayness of the peripapillary area. On the 42d day fundus photographs were taken again and showed normal fundi (Fig. 4*a* and *b*).

Right Lobe.—In the same monkey, nine days after the termination of the first experiment, another balloon, with capacity of 10 cc., was positioned over the right temporal area and 1 cc. of iodopyracet was inserted. On the second postoperative day the disc margins were blurred and there was slight edema of the peripapillary retina. Further increments of fluid were inserted into the balloon at intervals of two to five days. On the eighth day an increase in the edema of the disc and the peripapillary area was observed. On the 15th day a small splinter hemorrhage was seen inferior and medial to the right disc. On the 22d postoperative day the papilledema was resolving, and another 1 cc. of iodopyracet was inserted, making a total of 6.2 cc. in the balloon. On the 25th day the plastic cylinder came loose and the balloon gradually deflated. On the 28th day the fundi were normal except for accentuation of the striations of the layer of nerve fiber around the optic disc. The animal was killed with an overdose of pentobarbital sodium.

Necropsy Findings.—Necropsy disclosed a fibrous membrane around each balloon which was adherent to the dura and the arachnoid membrane. The cortex beneath the balloons was depressed about 1 cm. Gross cerebral edema was not evident, and the ventricles were not dilated. Histologic examination of the optic nerves revealed no evidence of inflammation or demyelination.

ANIMAL 2.—In another monkey, which weighed 6 kg., a balloon of 15 cc. capacity was inserted over the left temporal lobe. A total of 9.8 cc. of iodopyracet was inserted in increments over a period of 23 days. On the eighth day, after a total of 4 cc. had been inserted into the balloon, blurring of disc margins was observed. Peripapillary edema was noted on the 13th day. On the 19th day the edema appeared to be receding. Another 1.5 cc. of iodopyracet was inserted, and on the 21st day the pressure in the balloon was elevated to 27 mm. Hg. By this time there was definite bilateral papilledema, with slight elevation of the disc, blurring of margins, and peripapillary edema. On the 22d day the papilledema had receded, as had the pressure, which measured 13 mm. Hg. On the 23d day 0.6 cc. of fluid was inserted into the balloon, raising the pressure to 60 mm. Hg. The animal was dead three hours later.

At necropsy, both the cerebellum and the left uncinate gyrus were herniated and the right ventricle was dilated. The left optic tract and chiasm were markedly compressed and distorted. Histologic examination of the optic nerves revealed no evidence of inflammation or demyelination.

Results

Bilateral papilledema was produced in two monkeys by the gradual inflation of a subdural balloon over the temporal lobe. In one of these monkeys the papilledema receded, but it reappeared after the inflation of the balloon on the opposite side. Similar procedures were applied in four other monkeys without the production of papilledema. Included were six experiments in which the balloon was placed over temporal lobes and one experiment each in which the balloon was placed over frontal, parietal, and occipital lobes.

Why papilledema occurred in only two of the six monkeys could not be determined from the observations made.

Comment

Two methods for producing bilateral papilledema in monkeys have been reported previously: the injection of fluid intracranially under pressure and the insertion of sponge tents between the skull and the dura. Schieck [12] reported the production of papilledema in experiments employing the first method. Using this same method, Levinsohn [13] produced retinal hemorrhages, venous engorgement, and slight blurring of the disc margins but no appreciable elevation of the optic disc. Using the second method, Schieck [12] was unable to produce true papilledema. Parker,[6] who combined trephination of one eye with this second method, reported the production of marked papilledema in the trephined eye and low-grade papilledema in the opposite eye. We were not able to find reports of attempts to simulate intracranial lesions by inflation of intracranial balloons in monkeys.

The bilateral papilledema seen in Figure 3*a* and *b* is similar to that seen in man in association with intracranial lesions. Papilledema in man develops and recedes slowly over a period of days or weeks. This experimental papilledema likewise took about two weeks to develop and two or three weeks to subside. It is interesting to note that the cerebral compression produced by the subdural balloons in these experiments is analogous to the cerebral compression produced in man by a subdural hematoma. A finding of some interest was that in several instances the mean pressures recorded from the balloons in the animals in which no papilledema was observed were consistently as high as the mean pressures in the animals in which papilledema occurred (Fig. 5).

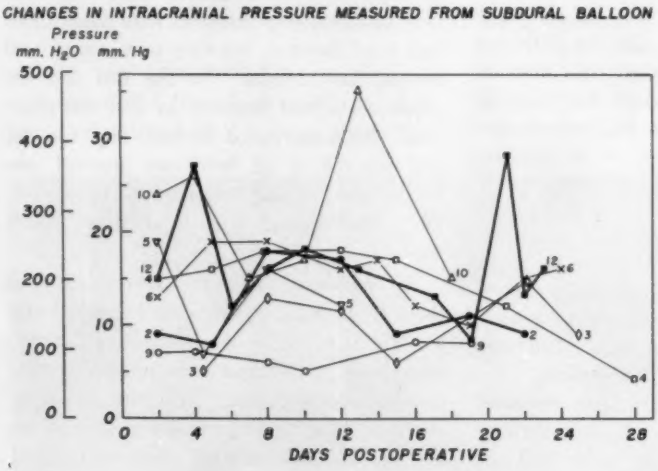

Fig. 5.—Graph demonstrating similarity of pressures recorded in experiments in which papilledema was observed (heavy lines) with experiments in which no papilledema was observed (thin lines). Numerals at beginning and end of lines are experiment numbers.

Summary

The mechanism of the production of papilledema in intracranial disease is inadequately understood in spite of extensive investigation. A review of the literature revealed a need for a method of producing in animals papilledema analogous to that observed in intracranial disease in man. Attempts to produce papilledema in dogs were unsuccessful. In two of six monkeys bilateral papilledema was produced by the gradual inflation of a subdural balloon. Fundus photographs documenting the presence and subsidence of papilledema are presented. Why papilledema occurred in some of the experiments but not in others could not be determined with the methods used.

Mayo Clinic.

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Tonometer Calibration

II. Ocular Rigidity

EARLE H. McBAIN, M.D., San Rafael, Calif.

Ocular rigidity is the term used to describe the relationship between pressure and volume changes in the eye. The rigidity of the eye is provided mainly by the sclera and cornea, which, however, are not completely unyielding but undergo an appreciable amount of stretching and contracting as a result of variations in the intraocular pressure. The application to the cornea of an impression tonometer, such as that of Schiøtz, produces a rather large change in pressure due to the weight of the instrument and the resulting displacement of intraocular fluid. Therefore, if the rigidity of the ocular coats can be shown to vary to any extent from eye to eye serious errors in interpretation of tonometer readings may result. This is true because tonometer conversion scales are based on an assumed average normal value for rigidity.

Friedenwald [1] determined that the data on rigidity of the eye obtained by Koster,[2] Ridley,[3] and Clark [4] seemed to fit a semilogarithmic formula of the following type:

$$K\frac{dV}{dP}=\frac{1}{P} \qquad (1)$$

transposing and integrating,

$$\log P=K_rV+C$$

where

P =pressure in millimeters of mercury

V =volume in cubic millimeters

K_r=coefficient of ocular rigidity when common logarithms are used

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Normal enucleated eyes were supplied for this study by the Stanford Eye Bank.

Division of Ophthalmology, Stanford University School of Medicine, San Francisco.

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A figure of K_r=0.0215 was used in the tonometer calibration formulas resulting in the tonometer scales of 1948. This value for K_r was derived from paired readings with 5.5 and 10.0 gm. weights made on 500 living eyes with a Schiøtz tonometer. Since Grant and Trotter's [5] measurements of rigidity on human enucleated eyes did not differ too much from this value, it was also used in the 1954 scale.[6]

Friedenwald made tables and nomograms based on this semilog formula and on an average normal value for K_r of 0.0215 for the purpose of determining when ocular rigidity was different from normal in the living eye. Paired readings with different weights on the eye were necessary. The use of these tables and nomograms clinically resulted in some confusion because of discrepancies in the calibration scales for different weights. For this reason, the 1954 scale was revised and has recently been published as the 1955 scale.[7] With use of this latest scale the discrepancies noted clinically in the 1954 scale seem to have been largely removed. However, the changes made in the 1955 calibration scale were not based on further laboratory work, but they consisted of empirical adjustments in certain of the formulas to make the scale fit a large number of recently made paired tonometer readings on living eyes using standardized tonometers. The formulas affected by these changes were those dealing with P_t (pressure while the tonometer rests on the eye) and V_c (volume of corneal indentation produced by the tonometer). The rigidity formula was not changed. The formula relating P_o (pressure in the undis-

turbed eye) to P_t, V_c, and K_r was the following:

$$\log P_o = \log P_t - K_r V_c$$

The author has shown that different values for the coefficients in the P_t formula for each tonometer weight are probably required. This differs from the previous use of the same coefficients for each P_t formula. This change results in relatively lower values for P_t with the heavier plunger weights than were used in the current scale. V_c data are also being collected in the present study and will be reported in the future.

The 1955 scale may be reasonably accurate for determining intraocular pressure with the various weights when the scale reading is between 3 and 7, for instance. This is, after all, what most ophthalmologists are interested in. It is possible, however, that the various formulas for P_t, V_c, and rigidity leading to the P_o scale may be erroneous when taken separately. It is important to correct any discrepancies which may exist in these formulas (1) to make the tonometer more accurate over the whole scale, (2) to make it possible to measure ocular rigidity clinically with more assurance, and (3) to increase the accuracy of tonography which is based on all of the tonometer calibration formulas.

Methods

Rigidity measurements were made in the first group of eyes of this study by the use of equipment previously described.[8] It consisted of a pressure transducer (strain gauge), recording potentiometer, and volume calibration reservoir. The strain gauge was connected to the enucleated human eye resting on a bed of cotton saturated with salt solution, by means of fine polyethylene tubing and a 22 gauge needle passing through sclera, posterior chamber, and pupil. Water manometers for calibration of the strain gauge were connected to the system by suitable stopcocks. The volume calibration reservoir used was the one devised by Grant[5] and consisted of an inverted 5 ml. centrifuge tube containing an air bubble of about 1.6 ml. The volume delivery of the tube was calibrated by weighing the fluid (0.9% NaCl) discharged when the air bubble was compressed by a known pressure and then allowed to discharge to room pressure. A curve of the pressure-volume relationship in the reservoir was developed by weighing the output from various pressures from 15 to 100 mm. Hg.

The above method of determining volume of fluid injected into the eye had the advantage of requiring inexpensive equipment, but it required recalibration for each eye and was possibly subject to errors due to change in room temperature during the experiment which might have changed the pressure in the air bubble. For this reason, the second group of eyes was measured with a different fluid-delivering device. This consisted of a microburette, accurate to 0.1 cu. mm., connected to the strain gauge by a short length of polyethylene tubing. By a quick twist of the micrometer screw it was possible to deliver a given amount (usually 5 to 15 cu. mm.) of fluid to the eye-strain gauge system in a fraction of a second. The amount of leakage from the burette, tubing, stopcocks, and strain gauge was never more than a small fraction of the outflow from the eye. Correction for the outflow and external leakage, if any, was made, as shown in Figure 1, by allowing the normal outflow curve to reestablish itself after the injection and then extrapolating a line back to the instant the injection was made. The same type of curve resulted from both methods of fluid injection.

The equipment used in this work was found to be very sensitive and to permit readings of pressure to the nearest 0.1 mm. Hg. Since a continuous recording of pressure was obtained, it was possible to make measurements of rigidity at any initial pressure with considerable accuracy.

Random measurements of rigidity showed an inverse relationship between K_r (as defined by Friedenwald's semilog formula) and the initial pressure and also between K_r and the quantity of fluid injected. In

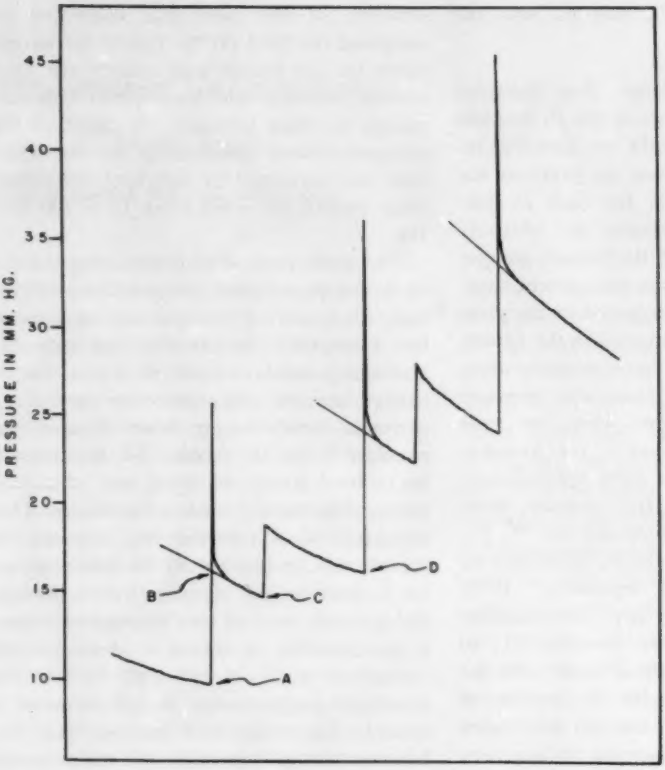

Fig. 1.—Copy from recorder showing method of measuring rigidity. The chart travels from left to right at 1 in. per minute. At Point *A* the injection of fluid is made. The pressure in the strain gauge rises abruptly and then falls rapidly as the fluid runs into the eye. The normal outflow resumes, and Point *B* is determined by extrapolation. The instantaneous change in pressure is the difference between *A* and *B*. At *C* the eye-strain gauge system is connected to the reservoir and the pressure is raised well above *B*. The normal outflow is allowed to resume until the pressure reaches *D*, which is approximately equal to *B*. Another injection is made at this point and the process is repeated.

order to investigate this finding more extensively, a continuous curve of pressure-volume relationship was constructed for the whole range of pressures. The measurements were begun at low pressures, and each succeeding injection was made at an initial pressure approximately equal to the final pressure of the preceding measurement (Fig. 1). The range of pressures investigated was from 5 to as high as 94 mm. Hg. In most cases the upper level of pressure was about 50 mm. Hg.

In some eyes the measurements were repeated several times at each pressure, and in others the whole curve was repeated both before and after the tonometer was applied to the eye for determination of P_t and P_o over the whole pressure range with each weight.

Measurements were also made by starting at high pressures and reducing the pressure before each succeeding injection. In the case of one eye fluid was withdrawn from the eye with the microburette for each measurement, with a starting pressure of 50 mm. Hg, and reduced in small steps.

Results

In every case the inverse relationship previously mentioned between rigidity and initial pressure was found. When log P was plotted as ordinate and V, as abscissa, a curve convex upward was obtained (Fig. 2). Since Friedenwald's coefficient of rigidity is the slope of this curve, one can see that the rigidity diminishes with increased pressure. Also, if measurements are made from the same initial pressure with the use of different volumes of fluid, the greater the volume the smaller the rigidity coefficient. When measurements were made with

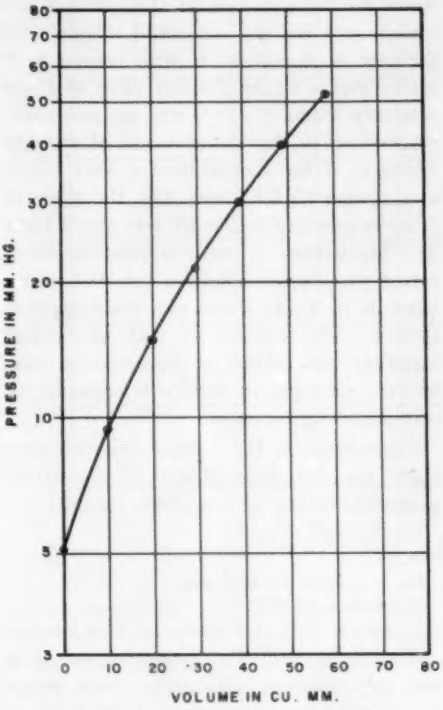

Fig. 2 (Eye 106).—Log P plotted against V.

descending initial pressure, whether by injection or withdrawal of fluid, the rigidity at low pressure was slightly increased, resulting in a slight exaggeration of the inverse relationship between K_r and initial pressure.

Table 1 shows the results of fitting the experimental data to two formulas. The semilogarithmic formula gave a rather poor fit for these data, as would be expected. The parabolic formula

$$P=a+bV+cV^2$$

(not shown in the Table) gave a considerably better fit. The best fit was obtained from the full logarithmic formula with the addition of a third constant to correct for the arbitrary selection of zero as the volume corresponding to the lowest pressure used in each experiment. This third constant (c) represents the theoretical change in volume necessary to reduce the pressure to zero. When log P was plotted against log $(V-c)$, a straight line resulted, with a very close fit (Fig. 3).

The formula involved is the following:

$$V=aP^b+c \qquad (2)$$

TABLE 1.—*Coefficients and Average Deviation for Two Different Formulas Fitted to Ten Eyes*

	1. log $P=A+BV$			2. $V=aP^b+c$ log $(V-c)=\log a+b \log P$			
Eye	A	B	Av. Deviation, %	a	b	c	Av. Deviation, %
23	0.741	0.0162	6.45	28.28	0.351	—48.8	0.52
24	0.811	0.0122	11.06	49.42	0.283	—78.3	0.58
25	0.773	0.0195	8.13	31.06	0.300	—51.0	0.46
27	0.837	0.0139	11.59	17.73	0.441	—37.1	0.43
101	0.779	0.0149	7.23	26.05	0.374	—47.9	0.19
102	0.711	0.0146	5.94	37.20	0.326	—60.7	0.33
103	0.784	0.0187	10.15	16.89	0.415	—33.6	0.30
104	0.847	0.0165	7.74	26.96	0.348	—51.0	0.31
105	0.709	0.0128	6.62	40.15	0.325	—69.8	0.06
106	0.788	0.0169	9.09	20.04	0.398	—38.7	0.37
			Geometric mean	27.77	0.353		
After stretching							
24	0.784	0.0148	7.86	27.66	0.367	—50.9	0.21
25	0.835	0.0158	15.21	22.33	0.367	—40.9	1.27
101	0.730	0.0160	9.73	25.47	0.360	—44.1	0.42
102	0.685	0.0167	11.95	24.39	0.373	—41.0	0.70
103	0.793	0.0194	9.83	18.12	0.390	—34.8	0.58
104	0.872	0.0176	7.16	18.72	0.399	—39.9	0.25
106	0.801	0.0180	11.67	13.29	0.461	—28.4	0.41

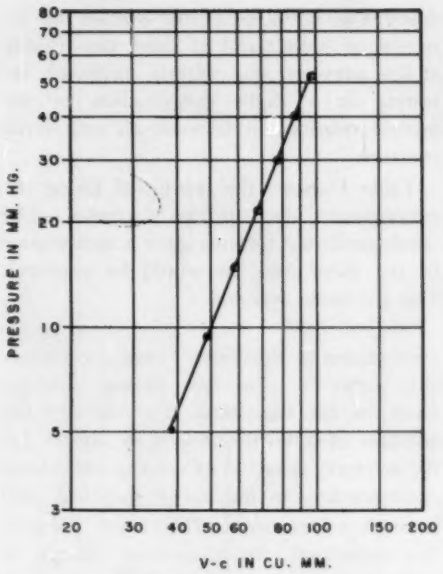

Fig. 3 (Eye 106).—Log P plotted against log $(V-c)$.

which may also be written (taking logarithms)

$$\log (V-c)=\log a+b \log P \qquad (3)$$

The experimental data were fitted to the formula by the method of least squares. First a table of values for P and V was made from a given series of measurements. Since the total volume of the eye was unknown and we are concerned mainly with the rate of change of V with respect to P rather than with the absolute value of V, an arbitrary value of $V=0$ was assigned, corresponding to the lowest value of P. For example, if the measurements were begun at a pressure of 5.1 mm. Hg, the value of V corresponding to $P=5.1$ was zero (Table 2). The volume of the first injection which raised the pressure from 5.1 to 9.4 in the example in Table 2 was put down opposite $P=9.4$. The volume of each succeeding injection was added to the previous ones and the total put in the Table opposite the corresponding pressure.

Corrections in the volume injected were made for the distensibility of the strain gauge and tubing by use of the formula

$$V_E=V_I-0.02\ (P_2-P_1)$$

where

V_E = volume reaching eye
V_I=volume injected
P_1 and P_2 = pressure before and after injection

The figure 0.02 was found by weighing the salt solution discharge from strain gauge and tubing after raising the pressure to a given amount and letting the system discharge to atmospheric pressure. In order to obtain enough fluid to weigh, it was necessary to open and close the proper stop-

TABLE 2.—*Data from One Eye (Eye 106) to Show Method of Calculation of Coefficients*

$$V=aP^b+c$$
$$\log (V-c)=\log a+b \log P$$

P_1=10 V_1=11.2
P_2=40 V_2=48.6
P_3=20 V_3=27.3

$$c=\frac{V_1V_2-V_3^2}{V_1+V_2-2V_3}$$

$$c=\frac{-200.97}{5.20}=-38.65$$

P	V	$V-c$	$\log (V-c)$	$\log P$	$V-c$ Calculated	% Deviation
5.1	0	38.65	1.58715	0.70757	38.34	−0.80
9.4	9.91	48.56	1.68628	0.97313	48.91	+0.72
14.8	19.62	58.27	1.76545	1.17026	58.60	+0.57
21.5	29.33	67.98	1.83238	1.33244	67.99	+0.01
30.0	39.05	77.70	1.89042	1.47712	77.64	−0.08
40.1	48.64	87.29	1.94096	1.60314	87.14	−0.17
51.8	58.08	96.73	1.98556	1.71433	96.49	−0.25
					Av. deviation=0.37	

By use of the method of least squares the coefficients a and b are calculated; $a=20.04$, $b=0.3981$.

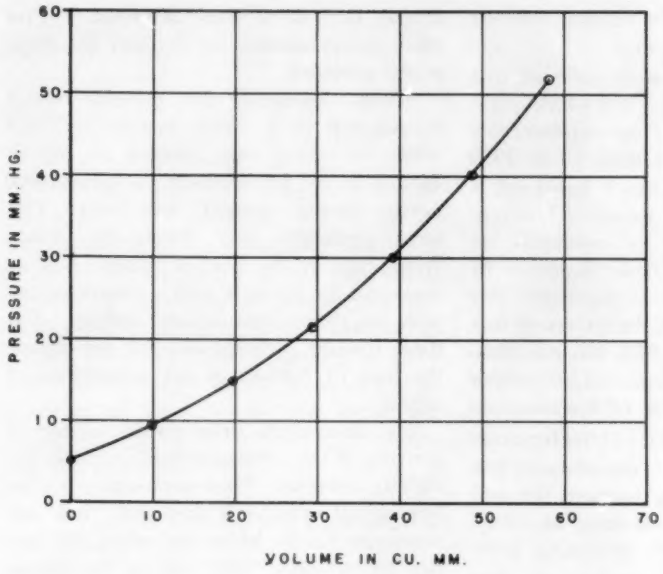

Fig. 4 (Eye 106).—Rectilinear plot of P versus V.

cocks several times, raising the pressure each time and allowing the fluid to accumulate in the weighing pan. This correction affected the results only very slightly but was included to maintain the maximum accuracy. Another small correction in the volume injected was made when the initial pressure of a measurement did not exactly equal the final pressure of the preceding one. This discrepancy was rarely more than 0.3 mm. Hg. Usually it was 0.1 or 0.2 mm. (For example, $V=\Delta V+0.1\times \Delta V/\Delta P$.) Figure 4 shows a rectilinear plot of P vs. V from Table 2.

To fit Equations 2 and 3 to the data of Table 2 it is first necessary to determine the value of coefficient c. On the curve of Figure 4 two points (P_1V_1) and (P_2V_2) are selected near the extremities. The geometric mean of the values of P_1 and P_2

$$P_3=\sqrt{P_1P_2}$$

is computed, and V_3 is read from the curve. All these points lie on the curve, therefore

$$V_1-c=aP_1^b$$
$$V_2-c=aP_2^b$$
$$V_3-c=aP_3^b$$
$$aP_3^b=\sqrt{aP_1^b\times aP_2^b}$$

or

$$V_3-c=\sqrt{(V_1-c)\ (V_2-c)}$$

from which

$$c=\frac{V_1V_2-V_3^2}{V_1+V_2-2V_3}$$

Values for $V-c$ are then computed and placed in the table. By use of Equation 3, which is in the form of a linear equation, it is then possible to calculate values for coefficients a and b by use of the method of least squares.

Inspection of Table 1 shows that the data from this study fit Equations 2 and 3 extremely well, as indicated by the average deviations of calculated from observed values of V. When plotted as log $(V-c)$ vs. log P, a straight line, as in Figure 3, results.

In order to determine the rate of change of V with respect to P in Equation 2 the following derivative is taken:

$$V=aP^b+c \qquad (2)$$

deriving,

$$\frac{dV}{dP}=abP^{b-1}$$

transposing and placing P in the denominator,

$$\frac{1}{ab}\times\frac{dV}{dP}=\frac{1}{P^{1-b}} \qquad (4)$$

When the exponent for P in differential Equation 4 is equal to unity, it is the same

equation as Friedenwald's rigidity Formula 1, with $1/ab$ being equal to K.

At one time Friedenwald believed that the data of Koster, Ridley, and Clark might better fit this equation if the exponent for P were somewhat larger than 1. In 1950 he published rigidity tables [9] based on a value of 1.25 for this exponent. Before the decennial report of the committee on tonometers of the American Academy of Ophthalmology and Otolaryngology, this data was reanalyzed and the exponent was found to be about 1.05. Since this was close to 1.0, the original semilogarithmic formula was used in the 1954 and 1955 scales.

The exponent for P $(1-b)$ in Equation 4 from the present data is considerably less than unity, usually lying between 0.6 and 0.7. This represents a decrease in coefficient of rigidity K_r with increasing pressure, as pointed out earlier in this discussion. These findings are directly opposite to those of Perkins and Gloster [10] in the rabbit eye, where the rigidity coefficient was found to increase with increasing pressure. However, Perkins and Gloster [11] stated that their preliminary results on human eyes suggested a different type of variation from that found in the rabbit eye.

Macri et al.[12] found K_r of cat eyes to increase with rising pressure until the pressure reached 30 to 35 mm. Hg. At this point K_r began to decrease as the pressure was elevated further. When the relationship of ΔP to ΔV was plotted, a straight line resulted at pressures above 30 mm. Hg (showing that the cat eye obeys Hook's law within that range).

MacDonald,[13] presumably using the 1954 scale, reported on the results of 24-hour tension studies involving tensions repeated at 2-hour intervals with 5.5, 7.5, and 10.0 gm. weights. He found abnormally high rigidity at normal pressures, which has since been found to be characteristic of the 1954 scale. However, when the pressure in the same eye rose to higher levels, the rigidity became normal, and at still higher pressures it was below normal. He concluded that there must be some inverse relationship between rigidity and the intraocular pressure.

Schiøtz measured the pressure-volume relationship in a single human eye, and when his data were plotted as log P against V by Friedenwald,[1] a pronounced curve, convex upward, was seen. This curve resembles very closely the curves from eyes in the present study. Schiøtz measured the pressure with a tonometer and took no precautions against leakage. For these reasons, Friedenwald did not include the data of Schiøtz in his calculations of rigidity.

The data which Friedenwald did use in arriving at the semilogarithmic formula for rigidity consisted of measurements on various animal eyes by Koster and Clark and measurements by Ridley on rabbit, pig, and two human eyes. Only one of the human eyes was normal. The other was glaucomatous. All of these eyes (except Koster's, which had been repeatedly stretched) were found to have extremely low rigidity (0.0015 to 0.007) when this was calculated with the semilog formula. This was presumably due to the fact that the loss of fluid from the eye due to normal outflow was disregarded by all the investigators except Ridley, who measured volume by counting the number of drops displaced from a closed chamber in which the eye was immersed. The development of a sensitive strain gauge and recorder and an accurate microburette has made it possible to increase greatly the accuracy of measurements of pressure and volume in the eye.

By use of Equations 1 and 4 it is possible to calculate the value of K_r for any pressure in a given eye when the coefficients a and b are known.

The method follows:

$$K\frac{dV}{dP}=\frac{1}{P} \qquad (1)$$

transposing,

$$\frac{dV}{dP}=\frac{1}{KP}$$

and

$$\frac{1}{ab}\times\frac{dV}{dP}=\frac{1}{P^{1-b}} \qquad (4)$$

transposing,

$\frac{dV}{dP}=\frac{ab}{P^{1-b}}$

therefore,

$\frac{1}{KP}=\frac{ab}{P^{1-b}}$

transposing,

$K=\frac{P^{1-b}}{ab\,P}$

simplifying,

$K=\frac{1}{ab\,P^{b}}$

For convenience in calculating values for K_r, Friedenwald used common logarithms, whereas the logarithms of calculus are natural or Naperian logarithms. Therefore, to convert K of the above equations to agree with Friedenwald's K_r, it is necessary to multiply the result by M (the factor for converting natural to common logarithms). (M equals 0.4343.)

Hence,

$K_r=\frac{M}{ab\,P^{b}}$ (5)

It is also possible to calculate the rate of change of K_r with respect to P by taking the derivative of Equation 5

$\frac{dK_r}{dP}=\frac{-M}{a\,P^{1+b}}$ (6)

Thus the results of the present study show that the coefficient of ocular rigidity as expressed in the semilogarithmic formula is not a constant at different pressures. Secondly, the rate of change of K_r with respect to P is also a variable. Table 3 shows values for K_r and dK_r/dP for various levels of P from each of the eyes studied.

TABLE 3.—*Friedenwald's Coefficient of Rigidity* K_r *and the Rate of Change of That Coefficient for Various Pressures Calculated from Formula 2 in Table 1*

		Pressure, Mm. Hg								
Eye	Formula *	5	10	15	20	25	30	40	50	60
23	K_r	0.0249	0.0195	0.0160	0.0133	0.0141	0.0133	0.0120	0.0111	0.0104
	dK_r/dP		−0.00068		−0.00027		−0.00016		−0.00008	
24	K_r	0.0197	0.0162	0.0145	0.0133	0.0125	0.0119	0.0110	0.0103	0.0098
	dK_r/dP		−0.00046		−0.00019		−0.00011		−0.00006	
25	K_r	0.0287	0.0233	0.0207	0.01895	0.0177	0.0168	0.0154	0.0144	0.0136
	dK_r/dP		0.00070		−0.00028		−0.00017		−0.00009	
27	K_r	0.0273	0.0201	0.0168	0.0148	0.0134	0.0124	0.0109	0.0099	0.0091
	dK_r/dP		−0.00089		−0.00033		−0.00018		−0.00009	
101	K_r	0.0244	0.0188	0.0162	0.0145	0.0133	0.0125	0.0112	0.0103	0.0096
	dK_r/dP		−0.00070		−0.00027		−0.00016		−0.00008	
102	K_r	0.0212	0.0169	0.0148	0.0135	0.0126	0.0118	0.0108	0.0100	0.0094
	dK_r/dP		−0.00055		−0.00022		−0.00013		−0.00007	
103	K_r	0.0317	0.0238	0.0201	0.0178	0.0163	0.0151	0.0134	0.0122	0.0113
	dK_r/dP		−0.00099		−0.00037		−0.00021		−0.00010	
104	K_r	0.0265	0.0208	0.0181	0.0164	0.0151	0.0142	0.0129	0.0119	0.0112
	dK_r/dP		−0.00072		−0.00028		−0.00016		−0.00008	
105	K_r	0.0196	0.0158	0.0138	0.0126	0.0117	0.0110	0.0101	0.0094	0.0088
	dK_r/dP		−0.00051		−0.00020		−0.00012		−0.00006	
106	K_r	0.0287	0.0218	0.0185	0.0165	0.0151	0.0141	0.0125	0.0115	0.0107
	dK_r/dP		−0.00087		−0.00033		−0.00019		−0.00009	
After stretching										
24	K_r	0.0237	0.0183	0.0158	0.0142	0.0131	0.0122	0.0110	0.0102	0.0095
	dK_r/dP		−0.00067		−0.00026		0.00015		−0.00008	
25	K_r	0.0294	0.0228	0.0197	0.0177	0.0163	0.0152	0.0137	0.0126	0.0118
	dK_r/dP		−0.00084		−0.00032		−0.00019		−0.00009	
101	K_r	0.0265	0.0207	0.0179	0.0161	0.0149	0.0139	0.0126	0.0116	0.0109
	dK_r/dP		−0.00074		−0.00029		−0.00017		−0.00008	
102	K_r	0.0262	0.0202	0.0174	0.0156	0.0144	0.0134	0.0121	0.0111	0.0104
	dK_r/dP		−0.00075		−0.00029		−0.00017		−0.00008	
103	K_r	0.0328	0.0230	0.0213	0.0191	0.0175	0.0163	0.0145	0.0133	0.0124
	dK_r/dP		−0.00098		−0.00037		−0.00021		−0.00010	
104	K_r	0.0305	0.0231	0.0197	0.0175	0.0161	0.0149	0.0133	0.0122	0.0113
	dK_r/dP		−0.00092		−0.00035		−0.00020		−0.00010	
106	K_r	0.0338	0.0246	0.0204	0.0179	0.0161	0.0148	0.0130	0.0117	0.0108
	dK_r/dP		−0.00113		−0.00041		−0.00023		−0.00011	

* $K_r=\frac{M}{ab\,P^{b}}$; $\frac{dK_r}{dP}=\frac{-M}{a\,P^{1+b}}$

The variation in K_r from eye to eye at a given pressure agrees with Grant's figures from enucleated eyes and leads one to suspect that there may be considerable variation in living eyes as well. This is especially true because of the accumulating evidence that rigidity is very much the same in living and freshly enucleated eyes.[10-12]

The effect of repeatedly raising the pressure to 50 mm. Hg or more is shown in Table 3. A slight increase in rigidity frequently results with no change in the general form of the curve.

The value of dK_r/dP in Table 3 shows that at higher pressures (above 50 mm.) K_r changes much less rapidly than at lower pressures. However, the change in K_r between 10 and 50 mm. Hg, the most important range clinically, is very appreciable.

It is possible to show the effect of substituting the rigidity data from the present study for those which were used in compiling the 1955 tonometer calibration. In making the 1955 scale Friedenwald used a large number of paired tonometer readings made on living eyes by Kronfeld, Ballantine, and Grant and Trotter. By adjusting the formulas for P_t and V_c, the various plunger weights were made to give the same value for P_o at the average scale reading. For instance, 1154 readings were made with the 5.5 and 10.0 gm. weights. The average scale reading was 5.39 with the 5.5 gm. weight and 10.10 with the 10.0 gm. weight. The intraocular pressure P_o from the 1955 calibration is 16.18 and 16.19 at each of the above scale readings.

When rigidity Equation 2 is substituted for the semilogarithmic formula, the equation relating P_o, P_t, and V_c is

$$V_c = aP_t^b - aP_o^b$$

solving for P_o,

$$P_o = \left(P_t^b - \frac{V_c}{a}\right)^{1/b} \qquad (7)$$

In Table 4 values for P_o are shown at the above-mentioned average scale readings for the 5.5 and 10.0 gm. weights. The figures from the 1955 calibration are shown in the first row. In the second row P_o for each weight is shown when Equation 7 is used. Coefficients a and b were determined for this calculation by taking the geometric mean of the values for a and b from 10 eyes. P_t and V_c figures were taken from the 1955 scale. The pressure P_o is considerably higher in this case, and it is 3.08 mm. Hg higher with the 10.0 gm. weight than it is with the 5.5 gm. weight. The higher value for P_o, when measured with the 10.0 gm. weight, is due to the fact that the heavier plunger load produces a larger change in pressure and therefore K_r, from the present data, is lower.

It is interesting to find that this discrepancy between weights is largely removed by using my P_t data [8] in place of P_t from the 1955 scale. The result appears in the third row of Table 4. These values of P_o are somewhat high. Considerable evidence exists that the average normal pressure of the human eye is about 15 or 16 mm. Hg.[14]

The abnormally high values for P_o noted here could be due to a reduction in rigidity of the eye following enucleation. Grant et al.[5] found such a decrease in rigidity in rabbit eyes. However, Perkins and Gloster [10] found the rigidity of dead eyes of rabbits to be equal to or greater than that of living eyes. Macri et al.[12] found no change in cat eyes. In any case, the change is apparently not great enough to account

TABLE 4.—*Values of* P_o *at Average Scale Readings of Paired 5.5 and 10.0 Gm. Weights*

	P_o from 1955 Tonometer Calibration	P_o Using Present Rigidity Data & P_t & V_c from 1955 Calibration	P_o Using Present Rigidity Data, My P_t Data, & V_c from 1955 Calibration
5.5 gm. weight scale reading 5.39	16.18	19.98	19.39
10.0 gm. weight, scale reading 10.10	16.19	23.06	19.88

TABLE 5.—*Coefficients and Average Deviation for Same Data as Table 1 when* b=*0.35* *

Eye	a	b	c	M/a, or E	Av. Deviation, %
23	28.38	0.35	—48.8	0.0153	0.52
24	32.65	0.35	—57.2	0.0133	0.60
25	22.92	0.35	—40.3	0.01895	0.28
27	29.34	0.35	—53.4	0.0148	1.08
101	29.86	0.35	—42.9	0.0145	0.18
102	32.17	0.35	—54.0	0.0135	0.46
103	24.40	0.35	—44.2	0.0178	0.96
104	26.48	0.35	—50.2	0.0164	0.29
105	34.47	0.35	—62.2	0.0126	0.18
106	26.31	0.35	—47.3	0.0165	0.80

* $V=aP^b+c$.

for the entire discrepancy in P_o observed here.

Another possible cause of this high value for P_o could be that the estimates of V_c which have been used in the calibration scale of 1954 and 1955 are too low. A preliminary inspection of the V_c data from the present strain-gauge measurements indicate that this may well be the case. These measurements of V_c are 25% to 50% higher than those of the 1954 and 1955 scales. A detailed report on the V_c data is forthcoming.

Conclusions

There can be little doubt that the relationship between pressure and volume changes in the human eye can be adequately expressed by means of the differential equation.

$$K\frac{dV}{dP}=\frac{1}{P^n} \qquad (8)$$

In the Friedenwald semilogarithmic formula, which has been used in the tonometer calibrations of 1948, 1954, and 1955, n in Equation 8 is equal to 1. The data from the present strain-gauge measurements fit this equation only if n or $1-b$ is considerably less than 1 (between 0.6 and 0.7 in most cases). This means that the rigidity coefficient K_r decreases with increasing pressure instead of remaining constant.

It is unfortunate that the equation which results from these experiments is so complex. Two coefficients are required, and it is not possible to express the rigidity of the eye by a single number. However, if n or $1-b$ were found not to vary too much from eye to eye one could perhaps assign a constant value to it and then let the other coefficient show the relative rigidity of each eye.

The geometric mean of the values of b from 10 eyes is 0.35. Table 5 shows the result of changing the coefficient b in the equation for each eye to 0.35. The value for a is determined by the method of least squares to give the best fit for the data.

TABLE 6.—K_r *for Various Pressures Calculated from Formulas in Table 5.*

	Pressure, Mm. Hg								
Eye	5	10	15	20	25	30	40	50	60
23	0.0249	0.0195	0.0169	0.0153	0.0141	0.0133	0.0120	0.0111	0.0104
24	0.0216	0.0170	0.0147	0.0133	0.0123	0.0116	0.0104	0.0097	0.0091
25	0.0308	0.0242	0.0210	0.01895	0.0175	0.0165	0.0149	0.0138	0.0129
27	0.0241	0.0189	0.0164	0.0148	0.0137	0.0129	0.0116	0.0108	0.0101
101	0.0237	0.0186	0.0161	0.0145	0.0135	0.0126	0.0114	0.0106	0.0099
102	0.0220	0.0172	0.0149	0.0135	0.0125	0.0117	0.0106	0.0098	0.0092
103	0.0289	0.0227	0.0197	0.0178	0.0165	0.0155	0.0140	0.0129	0.0121
104	0.0267	0.0209	0.0182	0.0164	0.0152	0.0142	0.0129	0.0119	0.0112
105	0.0205	0.0161	0.0139	0.0126	0.0117	0.0109	0.0099	0.0092	0.0086
106	0.0268	0.0211	0.0183	0.0165	0.0153	0.0143	0.0130	0.0120	0.0113

The deviation of calculated values of V from experimental values is increased somewhat in some of the eyes, but in no case is the change very great. Table 6 shows K_r calculated for various pressures with the use of these new equations. A comparison of Tables 3 and 6 reveals the extent of the change in K_r which is produced by substituting the figure 0.35 for the originally determined value of b. It can be seen that there is no change in K_r when P equals 20 mm. Hg.

In order to make the rigidity coefficient of this new expression have the same significance as K_r, which is already familiar, one can take the reciprocal of a and multiply it by M (the factor for converting natural to common logarithms). The values for M/a are also shown in Table 5.

It is a very interesting coincidence that this quantity (M/a) is numerically identical with K_r for the same eye when P equals 20, because from Equation 5

$$K_r=\frac{M}{a}\times\frac{1}{bP^b} \qquad (5)$$

when P equals 20,

$$\frac{1}{0.35(20)^{0.35}}=1.00$$

and

$$K_r=\frac{M}{a}$$

In this fashion, a new coefficient of ocular rigidity is obtained which is comparable with Friedenwald's coefficient, although the formula is different. The coefficient is determined as follows:

$$V=aP^b+c \qquad (2)$$

which becomes, when b equals 0.35,

$$V=aP^{0.35}+c$$

After transposing we have

$$\frac{1}{a}=\frac{P^{0.35}}{V-c}$$

Multiply both sides of the equation by M, and

$$\frac{M}{a}=M\left(\frac{P^{0.35}}{V-c}\right)$$

Let M/a be equal to E, the accepted term for ocular rigidity, and

$$E=M\left(\frac{P^{0.35}}{V-c}\right)$$

If we wish to determine the value of E by injecting a known quantity of fluid into the eye,

$$P^{0.35}=P_2^{0.35}-P_1^{0.35}$$

where

P_1 and P_2=intraocular pressure before and after the injection

Also

$$V-c=(V_2-c)-(V_1-c)$$

where

V_1 and V_2=volume of the eye before and after the injection

Then

$$V-c=V_2-V_1$$

or

$$V-c=\Delta V\text{ (volume of injection)}$$

The equation for ocular distention then becomes

$$E=M\left(\frac{P_2^{0.35}-P_1^{0.35}}{\Delta V}\right) \qquad (9)$$

By similar reasoning, the equation for tonometry is

$$E=M\left(\frac{P_t^{0.35}-P_e^{0.35}}{V_c}\right) \qquad (10)$$

The above equations are hardly more complicated than the Friedenwald equations, with the logarithmic expression being replaced by the exponential. This simplification is the result of assuming that the exponent b can be called a constant without producing significant inaccuracy. The validity of this assumption will depend upon further laboratory and clinical measurements. The equations can be simplified further by leaving out the factor M, which was introduced merely to show the numerical relationship with Friedenwald's coefficient.

Before making nomograms and tables for the purpose of adapting Equation 10 to the clinical measurement of rigidity and tonography, it will be necessary to revise or confirm the estimate of V_e.

Summary

Strain-gauge measurements of ocular rigidity on normal enucleated human eyes showed an inverse relationship between Friedenwald's coefficient and the intraocular pressure.

A close fit for the experimental data was found, with an exponential or a full logarithmic formula having two significant coefficients. By giving one of the coefficients the same value for all eyes it may be possible to express the rigidity of the eye by

a single number without introducing an appreciable inaccuracy.

1530 5th Ave.

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Metastatic Carcinoma of the Iris and Ciliary Body

JAMES R. DUKE, M.D., and JOHN J. KENNEDY, M.D., Baltimore

Introduction

Metastatic carcinoma to the anterior ocular segment occurs infrequently. Middleton [5] in 1952 found 31 cases in the literature and added 2 cases of his own. Mayer and Ray [4] in 1955 added one more case, and Bonamour and Bonnet [1] in 1956 added the last-reported case, bringing the total of such cases to 35.

The difficulties encountered in the clinical diagnosis of this condition plus the rarity of occurrence of the lesion itself prompts us to report the following four cases.

Report of Cases

CASE 1.—A 49-year-old Negro man entered a local hospital on Sept. 10, 1956, with the chief complaint of a constant cutting pain between his shoulder blades and sternum of four weeks' duration. There had been a weight loss of 30 lb. over an indefinite period.

Initial examination revealed a malnourished, chronically ill Negro man. Positive findings included a lag on inspiration of the left chest, signs of atelectasis in the left upper lobe, and, on x-ray examination, a rather ill-defined infiltration of the upper two-thirds of the left lung field.

One month after admission he developed hoarseness, and indirect laryngoscopy revealed a partial paralysis of the left vocal cord. On Oct. 29, 1956, left exploratory thoracotomy revealed in the hilus of the left upper lobe a stony-hard tumor mass which extended into the mediastinum. Biopsy of this mass was reported as revealing bronchogenic carcinoma, epidermoid type (Fig. 1). On Nov. 16, 1956, the patient was transferred to another hospital for x-ray therapy.

On Jan. 14, 1957, the patient, still hospitalized, was seen by the ophthalmologist,

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From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital.

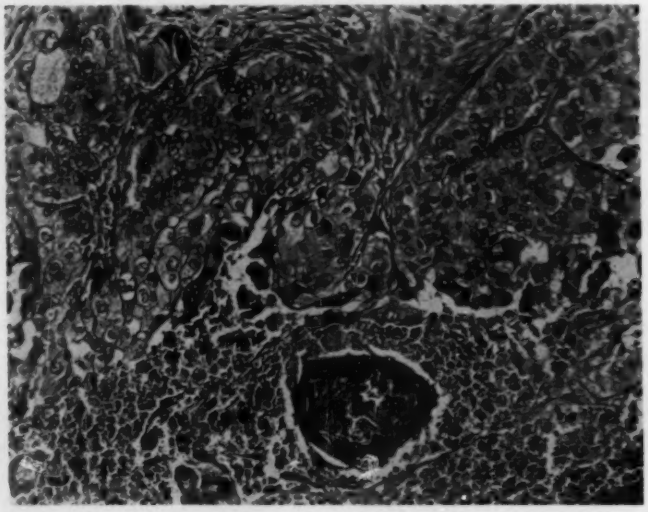

Fig. 1 (Case 1).—Biopsy specimen of bronchogenic carcinoma found at thoracotomy. Hematoxylin and eosin; × 120.

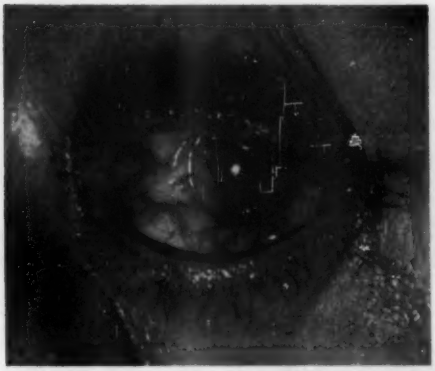

Fig. 2 (Case 1).—Appearance of eye after moderation of inflammatory signs. Note mass on iris nasally.

with the complaint that the left eye had been painful and red for six days. During this time the patient had noted photophobia and decreased vision in the left eye. Examination of the left eye revealed a visual acuity of 10/200. The lids were swollen. The conjunctiva was injected. The pupil was fixed and small, and a white opacity was noted in the nasal aspect of the anterior chamber. The intraocular tension was 22 mm. Hg (Schiøtz). On slit-lamp examination the anterior chamber was filled with a fibrinous exudate, principally inferiorly and nasally. The aqueous ray was 2+, and some pigment was noted on the anterior surface of the lens. The media were too cloudy for clear visualization of the fundus, but the optic disc appeared to be normal. The initial impression was iridocyclitis, fibrinous, acute, left eye. The condition was treated with mydriatics and local instillation of cortisone.

When the eye was reexamined four days later the inflammatory signs had abated somewhat and a white mass was visible on the iris near its base in the upper nasal quadrant (Fig. 2). The presence of this iris mass suggested the possibility of metastatic tumor. This impression was strengthened as the mass increased in size with time. The patient's general condition rapidly deteriorated, and he died on Feb. 12, 1957.

At autopsy a large partially necrotic tumor mass replaced the left upper lobe of the lung. There were numerous metastases to regional and distant lymph nodes, omentum, liver, and kidneys.

The left eye was also examined. At the limbus the conjunctival epithelium was elevated by a large mass of tumor cells of epithelial origin, which were aggregated in nests or cords and supported on a fibrous stroma (Fig. 3). These tumor cells exhibited a considerable degree of pleo-

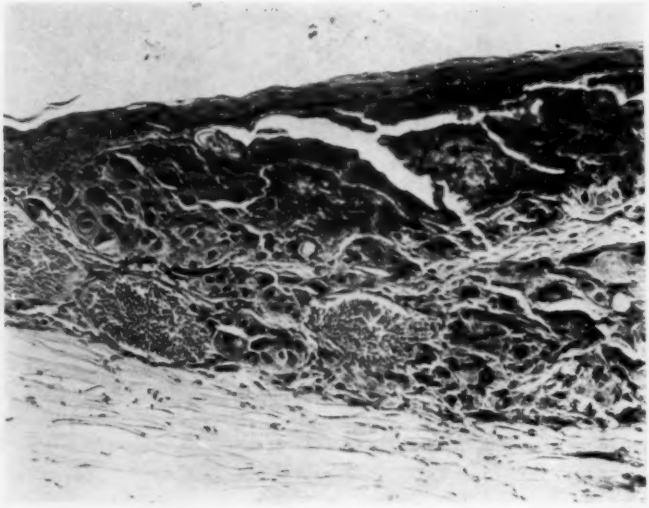

Fig. 3 (Case 1).—Metastatic bronchogenic carcinoma beneath conjunctival epithelium at limbus. Hematoxylin and eosin; × 120.

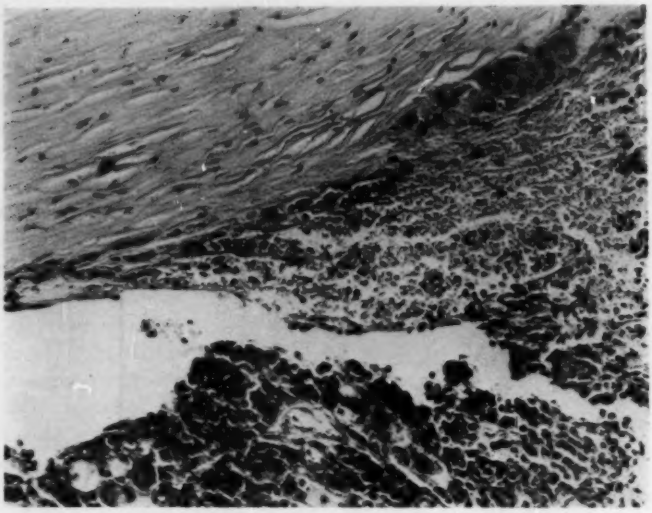

Fig. 4 (Case 1).—Metastatic bronchogenic carcinoma infiltrating root of iris and trabecular spaces. Hematoxylin and eosin; × 120.

morphism. Many possessed an abundant pink-staining cytoplasm, and most of the nuclei were large, with a prominent chromatin network. Mitotic figures were numerous. Similar sheets of tumor cells lined the posterior surface of the cornea peripherally; infiltrated the trabecular spaces, the canal of Schlemm, and the deep scleral plexus, and some cells extended out into the episcleral location just described (Fig. 4). Large masses of tumor cells were aggregated on the anterior surface of the iris, and other large masses of cells were located within the stroma of the iris itself (Fig. 5). Here they were arranged in nests which occasionally had a pink amorphous center suggesting keratinization. Many of the tumor masses within the iris were necrotic. In one area there had been extensive infiltration of tumor cells into the ciliary body, with extension throughout the pars plana noted in the same sections.

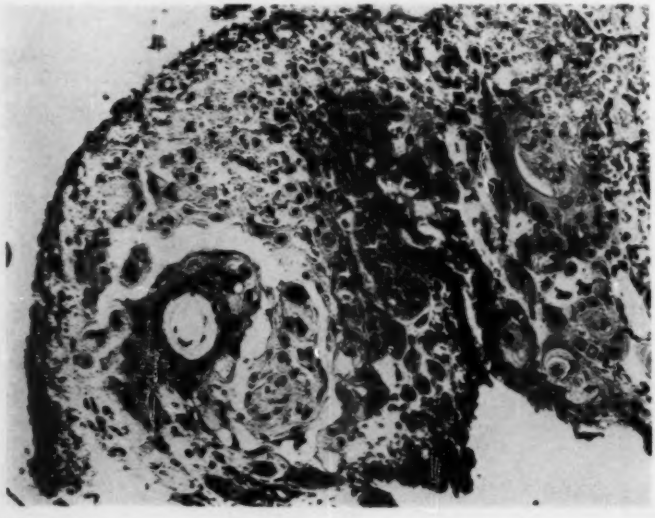

Fig. 5 (Case 1).—Metastatic bronchogenic carcinoma within stroma of iris. Hematoxylin and eosin; × 120.

The choroid was not involved. The cellular pattern of the tumor tissue within the eye corresponded closely with that of the primary tumor in the lung.

The pathologic diagnosis was carcinoma, epidermoid bronchogenic, metastatic to the iris, ciliary body, and limbus.

CASE 2.—A 54-year-old white man was first examined at The Johns Hopkins Hospital on Jan. 9, 1956, with the chief complaint of a foreign body in the right eye.

The family history disclosed that a sister had died of tuberculosis in 1930. The patient himself had in 1933 developed fibrocaseous infiltrates of the left upper lung, which by 1939 had spread to involve all of the left lung and upper half of the right lung. Between 1939 and July, 1955, these pulmonary lesions remained unchanged. In 1948 a bladder tumor was diagnosed at another hospital. Before treatment could be initiated, he was transferred to a mental hospital for an acute episode of schizophrenia. In 1950 he reappeared at the first hospital with complaints of hematuria, frequency, and nocturia. Cystoscopy revealed a tumor at the base of the bladder and on the vesical neck. Two transurethral resections of the tumor were done in October and November, 1950. Pathological diagnosis was "papillary transitional-cell carcinoma of the bladder."

On July 7, 1955, the patient was first seen by an ophthalmologist, at which time he complained of pain and decreased vision in the right eye of two and one-half weeks' duration. The vision was reduced to counting fingers at 1 ft. The eye was congested; the cornea, steamy, and in the deep anterior chamber there was a 2 mm. hyphema. There was a question of rubeosis of the iris above, though the steamy cornea prevented accurate visualization. The tactile tension was elevated. One week later the visual acuity had improved to 20/50 and the eye was less congested. Tactile tension was still elevated. On slit-lamp examination there were large keratic precipitates centrally, a positive aqueous flare, fibrin in the anterior chamber, and posterior synechiae. In the iris stroma at 12 o'clock was a large translucent nodule covered with blood vessels. Ophthalmoscopic examination disclosed no gross lesions in the fundus. The clinical impression was granulomatous uveitis, possibly tuberculous in etiology. It was stated, however, that tumor of the iris should be ruled out.

Six months later, Jan. 9, 1956, he was first seen at The Johns Hopkins Hospital, complaining of a foreign body in his right eye. Visual acuity was reduced to light perception. Significant findings included elevated tactile tension; conjunctival injection, most marked in the upper outer quadrant of the globe; a steamy cornea with a central area which stained with fluorescein; a 3 mm. hyphema, and a whitish vascularized mass in the iris between 9 and 12 o'clock. Clinical impressions varied between endophthalmitis secondary to a perforating corneal ulcer and active granulomatous uveitis. However, one observer listed intraocular tumor among the possible diagnoses.

On Jan. 14, 1956, the right eye was enucleated. On microscopic examination a considerable degree of fresh hemorrhage and moderate numbers of inflammatory cells were noted within the anterior chamber. Also present were several large clumps of cells, fragments of a cellular mass, which had infiltrated one limb of the iris. The posterior surface of the cornea on this side of the section was lined by a thick layer of similar cells. These extended back to the chamber angle, completely filling it. The limb of the iris on this side was almost completely replaced by similar tumor cells (Fig. 6). The tumor cells were small, with a very scant pink-staining cytoplasm, and possessed small round, oval, or spindle-shaped nuclei (Fig. 7). Mitotic figures were rare. The tumor mass was supported on a thin strand of fibrous stroma. Large masses of the tumor cells were completely necrotic, and many polymorphonuclear leukocytes infiltrated this necrotic area. On the surface of the opposite limb of the iris there was

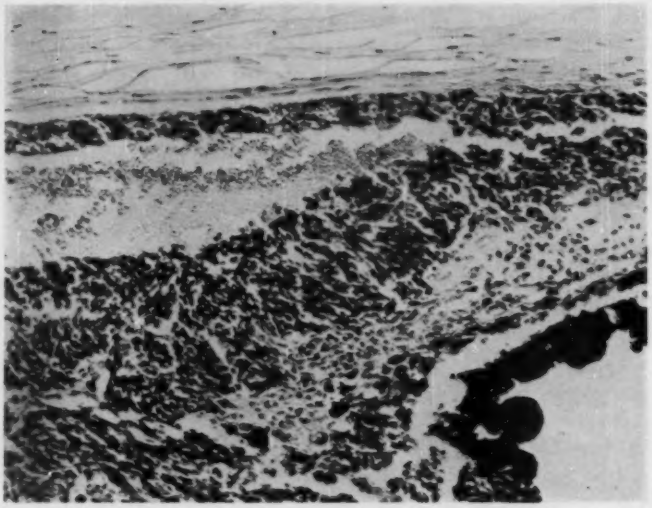

Fig. 6 (Case 2).—Metastatic bronchogenic carcinoma lining posterior surface of cornea and infiltrating iris stroma. Hematoxylin and eosin; × 120.

a delicate fibrovascular membrane, which extended back toward the chamber angle. The iris was in contact with the cornea in this region, resulting in blockage of the chamber angle. From the fibrovascular membrane there was fresh hemorrhage into the stroma of the iris as well as into the chamber angle. The ciliary body, free of tumor, was somewhat atrophic, with hyalinization of the ciliary processes. The choroid was not remarkable. Except for extensive peripheral cystoid degeneration, the retina appeared to be fairly well preserved. Some swelling and vacuolation of the nerve fibers as they entered the optic disc was noted. The lamina cribrosa was not depressed, but the optic nerve fibers for a short distance behind it had lost their myelin sheaths.

After considerable study it was decided that the iris tumor was not a primary malignant melanoma but an undifferentiated carcinoma metastatic to the iris. Additional

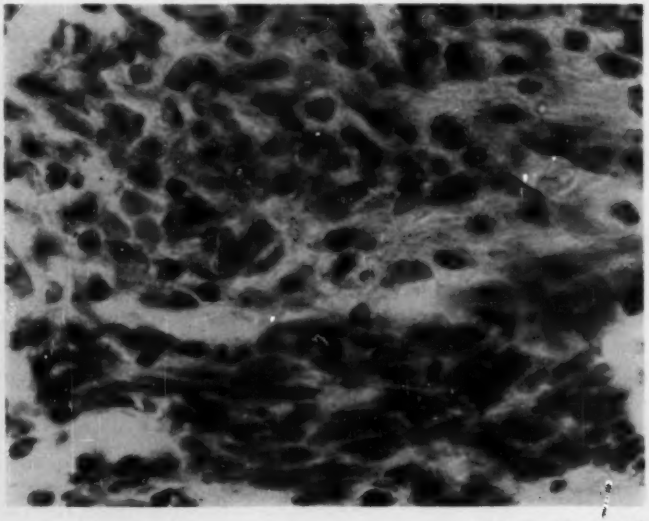

Fig. 7 (Case 2).—Morphology of metastatic tumor cells in iris stroma. Hematoxylin and eosin; × 725.

diagnoses were glaucoma, secondary, and hypopyon, the latter resulting from necrosis within the tumor.

The patient had been discharged and was thus lost for follow-up study until he was admitted to another hospital on April 23, 1956, with complaint of dull aching headache of about three weeks' duration. Chest x-ray revealed a nodular density in the right midlung field; it could be seen, in review of his old films, that this had first been present 10 months previously but had increased in diameter from 2.5 to 3.5 cm. It was thought that this lesion represented either a bronchogenic carcinoma or a metastatic lesion. The patient became increasingly lethargic and withdrawn. On May 22, 1956, a pneumoencephalogram was done. After this procedure, the patient went into shock and died. The final clinical impression was probable bronchogenic carcinoma with question of intracerebral metastasis.

At autopsy fibrous scars of the old tuberculous process were found in the lungs. In addition, there was in the lateral segment of the right middle lobe of the lung a nodule measuring 5×4 cm. in diameter, firm and yellow at its periphery and dark and spongy in the center. There was no adherence of the nodule to the bronchial tree. In the left lobe of the cerebellum beneath the dura was another 3×4 cm. firm yellow mass. The tonsils of the cerebellum had herniated into the foramen magnum.

Microscopic examination of the tumor in the lung revealed that it was composed of tumor cells arranged in large nests, filling the alveolar spaces (Fig. 8). The cells, of moderate size, possessed a moderate to scant amount of pink cytoplasm and nuclei which varied from round to oval in shape. The long spindle-shaped nuclei, seen in some areas of the iris tumor, were not encountered as frequently in the lung tumor. On the other hand, the cells comprising the lung tumor were more pleomorphic in appearance and mitotic figures were more frequent. Much dense fibrous scar tissue accompanied the nests of tumor cells. Similar nests of tumor cells were noted in the metastasis to the dura.

The final impression was that the primary oat-cell carcinoma arose in the lung, with metastasis to the iris and brain.

CASE 3.—A 59-year-old white man was first seen by the ophthalmologist in June, 1948, with the chief complaint of pain in the right eye of three days' duration.

The events antecedent to his ocular difficulties began in January, 1947, when a large bladder calculus was removed by the transurethral route. At that time it was noted in

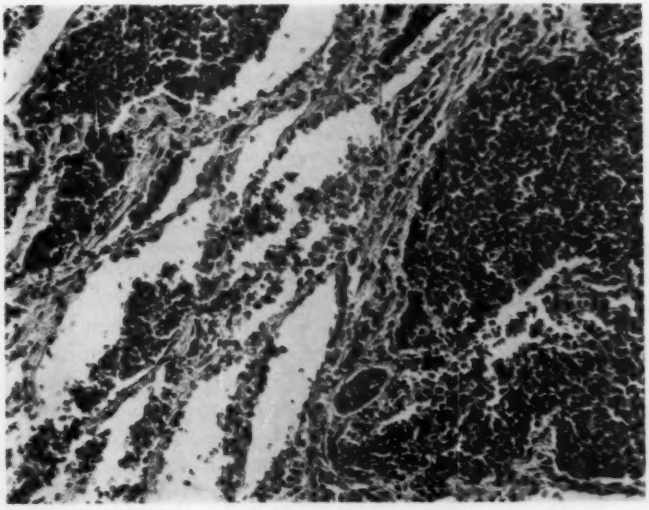

Fig. 8 (Case 2).—Bronchogenic carcinoma filling alveolar spaces in lung. Hematoxylin and eosin; × 120.

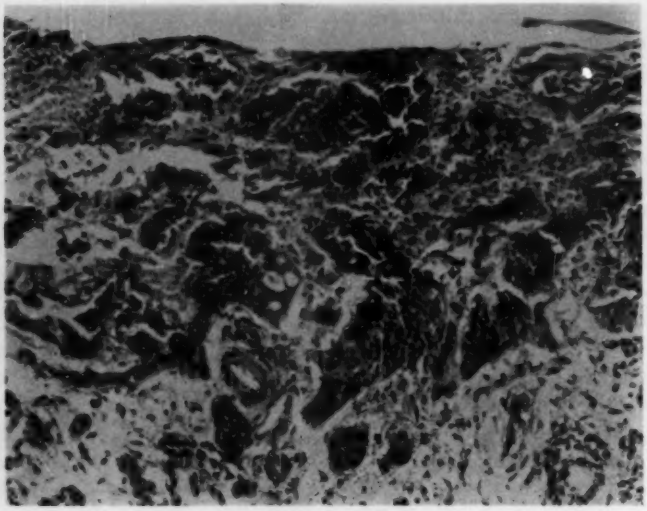

Fig. 9 (Case 3).—Transitional-cell carcinoma of bladder infiltrating submucosa of bladder wall. Hematoxylin and eosin; × 120.

the history that hoarseness had been present for many years. Hematuria continued. In September, 1947, biopsy of the bladder was inconclusive, the diagnoses varying between transitional-cell carcinoma and cystitis cystica glandularis. In May, 1948, at another biopsy of the bladder thansitional-cell carcinoma was diagnosed (Fig. 9). The tumor had infiltrated deeply into the submucosa and was composed of small nests or cords of cells, the cells being small with a moderate amount of cytoplasm and small oval or round nuclei. Mitotic figures were rare, and pleomorphism was not a prominent feature.

The patient then developed signs of congestive heart failure, which responded to digitalization. X-ray of the lungs in March, 1948, had disclosed prominent lung root shadows, and in more x-rays, in May, 1948, the generalized mottled appearance of both lung fields was commented upon.

On May 29, 1948, the right eye became red and painful, and the patient was seen by an ophthalmologist three days later. Ex-

Fig. 10 (Case 3).—Bronchogenic carcinoma metastatic to root of iris and chamber angle. Hematoxylin and eosin; × 120.

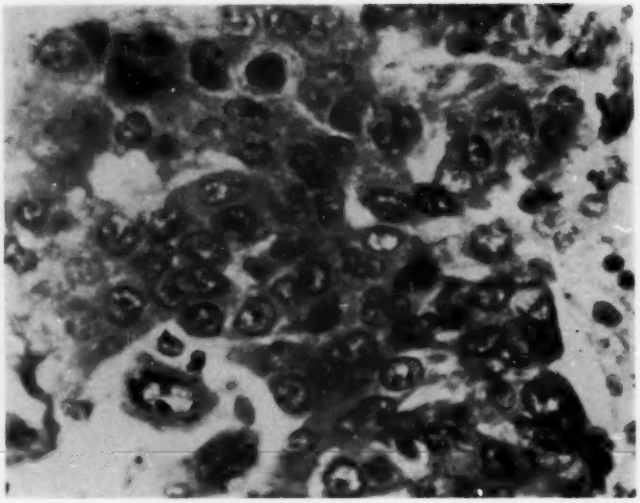

Fig. 11 (Case 3).—Morphology of metastatic tumor cells in iris stroma. Hematoxylin and eosin; ×725.

amination revealed a moderate degree of deep conjunctival injection between 5 and 7 o'clock near the limbus. A small irregular gray mass was noted in the anterior chamber at 6 o'clock at the root of the iris, and the iris behind this mass was depressed. On ophthalmoscopic examination an elevated mass was seen in the extreme periphery of the fundus, probably in the ciliary body, between 4 and 7 o'clock. The tumor was thought to be either a primary malignant melanoma of the ciliary body or a metastatic tumor to the ciliary body. The eye was enucleated on June 17, 1948.

Microscopic examination revealed in the anterior chamber a small amount of fibrin and a few polymorphonuclear leukocytes. Prominent were numbers of other larger cells, which apparently came from a large tumor mass. This mass had virtually replaced the ciliary body on one side of the section as well as a large portion of the base of the iris (Fig. 10). The tumor was composed of cells arranged in rather compact cords or nests. Occasionally, the tumor cells were arranged around a space, but there was no polarity of the cells which might have suggested acinar formation. The cells, large with abundant pink-staining cytoplasm and containing round or ovoid nuclei, varied considerably in size and shape (Fig. 11). Mitotic figures were frequently seen. Occasional interepithelial bridges were noted. Several large nests of cells were lying free in the posterior chamber. The chamber angle on the side of the tumor mass was, in many sections, completely closed. The choroid was not remarkable, and the retina showed only a moderate degree of peripheral cystoid degeneration. This carcinoma metastatic to the ciliary body and iris in no way resembled the biopsy material of the transitional-cell carcinoma of the bladder.

The patient gradually went downhill and died one month after enucleation.

At autopsy, a tumor arising from the main bronchus of the left lower lobe of the lung was found. This had extended to adjacent lung and had metastasized to the right lung; to peribronchial, peritracheal, periaortic, peripancreatic, and iliac lymph nodes; to the diaphragm, liver, duodenum, appendix, left kidney, and left adrenal. On microscopic examination the lung tumor, squamous-cell carcinoma in type (Fig. 12), very closely resembled the metastatic tumor in the ciliary body and iris of the right eye.

On the basis of these findings it was decided that the patient had had two primary tumors: one, a transitional-cell carcinoma of the bladder and, the second, a bronchogenic carcinoma. The latter tumor had metas-

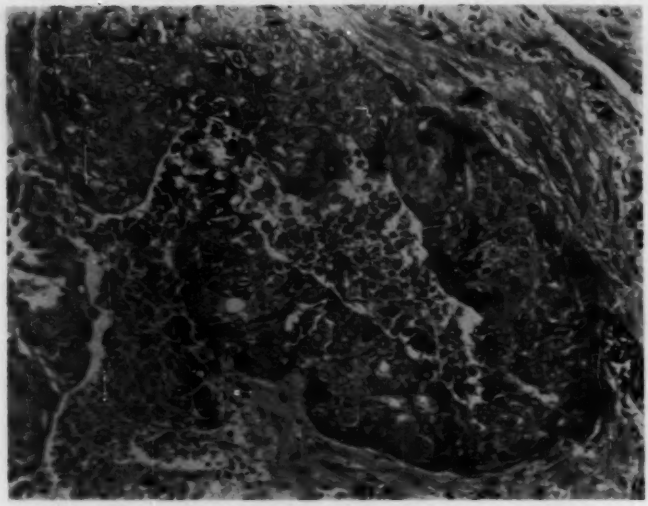

Fig. 12 (Case 3).—Morphology of the bronchogenic carcinoma within the lung. Hematoxylin and eosin; × 120.

tasized to many sites, including the iris and ciliary body of the right eye.

CASE 4.—A 67-year-old white man was first admitted to The Johns Hopkins Hospital on July 10, 1941, with a mass in the iris of the right eye. He had a chronic nonproductive cough of several months' duration, and for one month he had been aware of a mass in the right side of his neck. Also, for about a month he had noted a white spot in his right eye. The eye had been somewhat red at times, but there was no history of pain or of visual loss.

Physical examination revealed a mass of hard lymph nodes in the supraclavicular region on the right and large dilated veins over the upper thorax and arms, suggesting mediastinal obstruction. There were signs of atelectasis over the right lower lobe of the lung.

In the right eye, best corrected vision was 20/70−1. In the conjunctiva there were some prominent vessels. The nasal aspect of the iris was replaced by a pinkish lobulated mass in which many whorls of small blood vessels were noted. In places this mass was

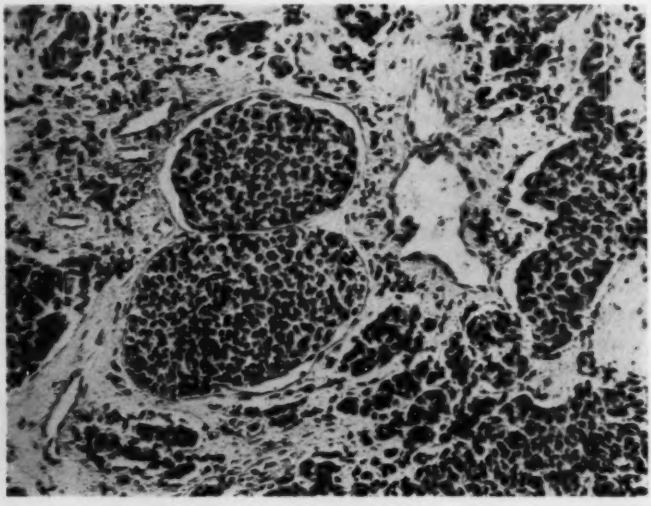

Fig. 13 (Case 4).—Partial replacement of supraclavicular lymph node by metastatic carcinoma, probably bronchogenic in origin. Hematoxylin and eosin; × 120.

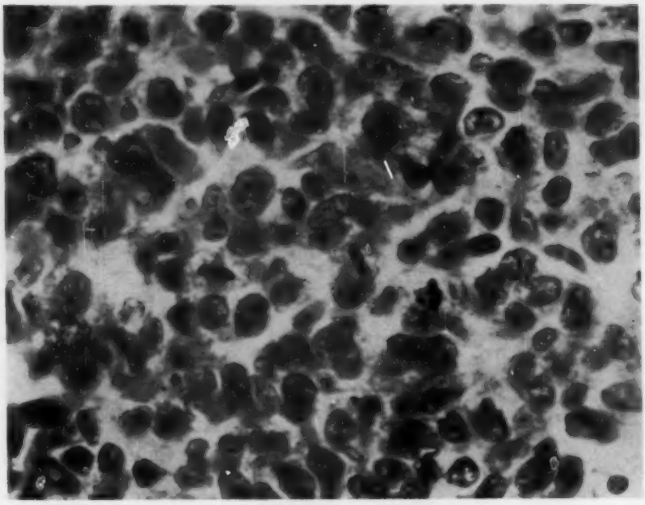

Fig. 14 (Case 4).—Morphology of metastatic tumor cells in iris stroma. Hematoxylin and eosin; ×725.

in contact with the posterior surface of the cornea and cells were seen floating in the anterior chamber. There was no aqueous ray. Pigment deposits were noted on the anterior surface of the lens, and there was a moderate degree of nuclear sclerosis. The intraocular tension was 35 mm. Hg (Schiøtz).

The clinical impression was bronchogenic carcinoma with metastasis to the right supraclavicular lymph nodes and the right iris.

Biopsy of a supraclavicular lymph node (Fig. 13) revealed that the node was almost completely replaced by closely packed epithelial tumor cells arranged in large nests or cords. The cells were of moderate size and contained a very scant pink-staining cytoplasm and round or oval nuclei, in which a chromatin network was prominent. Mitotic figures were numerous. Occasional areas of necrosis were present among the nests of tumor cells. Within some of the vascular channels in the supporting fibrocollagenous matrix tumor cells were frequently seen. The diagnosis was "carcinoma, metastatic in lymph node, probably primary in the lung."

As the right eye was causing the patient no discomfort, he was discharged. Three weeks later the eye became extremely painful and the patient was readmitted to the hospital. Examination revealed that vision was reduced to light perception. The large tumor had replaced the nasal aspect of the iris, and the temporal aspect showed marked superficial vascularization. At the bottom of the anterior chamber was a large gray amorphous mass of cells and fibrin. The intraocular tension was 54 mm. Hg. On Aug. 14, 1941, the right eye was enucleated. One month later the patient died. No autopsy was obtained.

Microscopic examination of the eye revealed a shallow anterior chamber practically filled with fibrin, a few red blood cells, masses of necrotic cells, and cells which seemed to arise from a mass in the iris. One limb of the iris was greatly thickened by a mass of cells, the majority of which were necrotic, although nests of apparently viable cells (Fig. 14) were seen at the pupillary margin and near the root of the iris (Fig. 15). The cells were arranged in long cords or nests and resembled the epithelial tumor cells described in the lymph node. Near the root of the iris the tumor cells were in direct contact with the posterior surface of the cornea, closing the chamber angle on this side of the section. Much of the iris pigment epithelium was necrotic, with liberation of pigment into the posterior chamber. The opposite limb of the iris was extremely thin

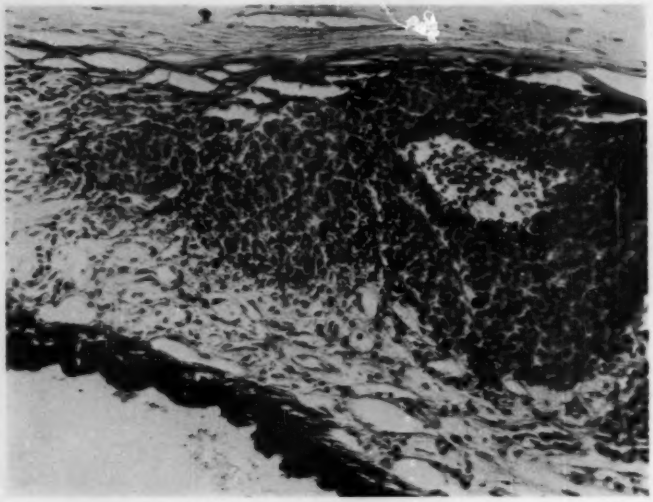

Fig. 15 (Case 4).—Carcinoma, probably bronchogenic in origin, metastatic to iris. Hematoxylin and eosin; × 120.

and atrophic, and on its anterior surface was a prominent fibrovascular membrane. The ciliary body and choroid were free of tumor. Toward the periphery rather extensive anterior synechiae closed the chamber angle. The retinal ganglion cells were moderately decreased in number. There was a localized detachment of the retina about the optic disc, with early degeneration of the rods and cones in this area of detachment. In addition, there was early edema of the optic papilla, and groups of nerve fibers at the disc margin and within the disc itself were noted to be swollen and took a rather bright eosinophilic stain.

The pathological diagnoses were carcinoma, metastatic, to the iris, probably primary in the lung; secondary glaucoma; peripapillary detachment of the retina, and papilledema, minimal.

Comment

While, statistically, there is a higher incidence of metastasis of tumor to the left eye than to the right eye,[2] in three of our four cases the metastasis involved the right eye. This involvement was limited to the iris in two cases (Cases 2 and 4), while in the other two the tumor was present in both iris and ciliary body. It is somewhat unexpected that in each of the four cases the primary carcinoma had originated in the lung. Middleton,[5] in his review of metastatic carcinomas involving the anterior ocular segment, found that among 28 cases in which the site of the primary tumor was known carcinoma of the breast accounted for 14, or half the cases. He found five cases in which the primary tumor was bronchogenic and added one of his own. Since then, one other has been reported,[4] bringing the total of previously reported cases to seven.

These four cases illustrate the pitfalls encountered in the interpretation of clinical findings. In Cases 1 and 2, the initial diagnosis was anterior uveitis, despite the fact that Case 1, at the time, was receiving radiation therapy for bronchogenic carcinoma. However, in both of these cases the inflammatory signs completely masked the presence of the tumor mass in the iris. When these inflammatory signs had subsided and the iris mass became visible, the correct diagnosis was made in the patient with known bronchogenic carcinoma (Case 1) and it was entertained, though only briefly, in Case 2. This latter patient, however, had had a long history of pulmonary tuberculosis, and tuberculous uveitis was considered the most probable diagnosis.

In each of these four cases the eye was injected and in Case 3, which lacked other inflammatory signs, the injection was localized to the affected quadrant of the globe. Recurrent hyphemas, stressed by Kreibig[3] as an important diagnostic point, as they rarely occur in granlomatous iritis, occurred in one of the four cases. However, in three of the cases fibrin and cells were noted in the anterior chamber. The mass itself was in each instance noted to be gray or white, and in three instances the vascularization of the mass was commented upon. In two of the cases (Cases 2 and 4) rubeosis in an area of the iris uninvolved by tumor was noted. In both of these eyes the intraocular pressure was elevated. Secondary glaucoma was probably present in Case 3 as well; though no tension was recorded, a wound, interpreted as a paracentesis wound, was found on microscopic examination of the globe.

In Case 4, although inflammation of the anterior ocular segment with secondary glaucoma was a prominent feature, the presence of enlarged supraclavicular lymph nodes on the affected side, coupled with the pulmonary findings, suggested, initially, the correct diagnosis, subsequently proved by lymph node biopsy.

Inflammatory signs in Case 3 were minimal, and the tumor mass involving the ciliary body as well as the iris was thought to be a malignant melanoma, though the possibility of metastatic tumor was considered. However, the patient was then in the hospital for treatment of a transitional-cell carcinoma of the bladder, a tumor which was considered very unlikely to metastasize to so distant a site as the eye. The patient died before the pathologic report of the enucleated eye was available, and it was not until autopsy that the completely unsuspected bronchogenic carcinoma with widespread metastases was discovered.

It is of interest that in three cases (Cases 2, 3, and 4) the metastatic tumor in the anterior ocular segment was the first clinical manifestation of the primary tumor in the lung. The length of survival after the appearance of the metastatic lesion varied from 1 month (Case 1) to 11 months (Case 2). In this latter case the presence of a primary lung tumor was not suspected until nine months after the occurrence of the initial ocular signs and symptoms.

Summary

Four cases in which metastatic carcinoma involved the anterior ocular segment are reported. The difficulties encountered in the clinical interpretation of attendent signs and symptoms are described. In each of these cases the diagnosis was verified by microscopic examination of the affected eye.

Wilmer Institute, The Johns Hopkins Hospital (5).

Addendum

Since this article was prepared for publication a report of two more cases of metastatic carcinoma of the iris has appeared.[6]

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Case Reports

Posterior Embryotoxon Associated with Slit-like Pupil and Corectopia

Report of an Interesting Case

MARVIN A. GARLAND, M.D., Chicago, and ROBERT L. SINGER, M.D., Fremont, Calif.

That condition which is now most commonly referred to as posterior embryotoxon has been listed in the literature of the cornea under many different names. Frequently used synonyms have included the terms posterior marginal corneal dysplasia,[1] peripheral refractile postcorneal rim,[2] and congenital hyaline membrane of posterior surface of the cornea.[3]

In an extensive study, Burian, Braley, and Allen[4] have demonstrated that this peripheral ring-shaped opacity of the cornea referred to as posterior embryotoxon usually is nothing but a very prominent anterior border-ring of Schwalbe. This anomaly either may occur as an isolated finding in otherwise essentially normal eyes or else may be associated with other malformations of the eye which usually involve the iris.[1] There may be abnormalities of the iris stroma, such as polycoria, corectopia, slit-like pupil, and hypoplasia of the iris stroma, or there may be anomalous peripheral iris processes present. These iris processes extend across the anterior chamber angle to insert on the prominent anterior border-ring of Schwalbe and trabecular meshwork, and, if numerous enough, they may cause glaucoma, through obstruction to aqueous outflow. Often, a familial tendency is associated with both embryotoxon and anomalies of the iris stroma.[5,6]

Submitted for publication April 28, 1958.

From the Department of Ophthalmology, Cook County Hospital, Chicago.

Report of Case

A 5-month-old Negro boy was brought to the eye clinic of the Cook County Hospital because his mother noticed irregularities of both pupils shortly after birth. The right eye had a vertical slit-like pupil that was displaced temporally (Fig. 1), and the left eye showed corectopia with displacement of the pupil inferiorly and nasally (Fig. 2). The periphery of both corneas

Fig. 1.—Close-up view of slit-like pupil, showing temporal displacement.

Fig. 2.—Corectopic pupil, showing inferior nasal displacement. The embryotoxon is visible just inside the limbus (arrow).

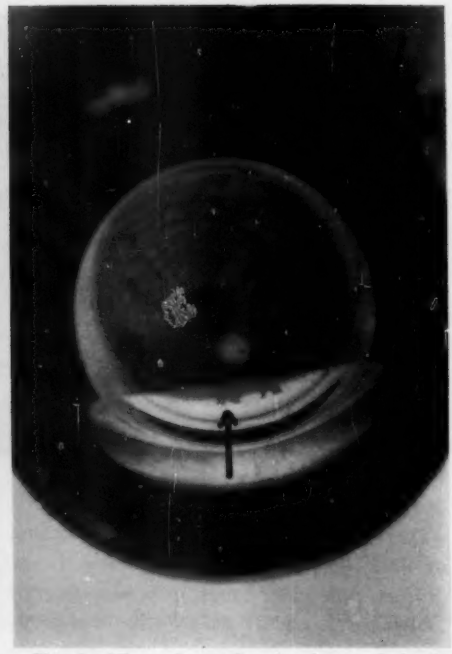

Fig. 3.—View of superior chamber angle in the left eye through a Goldmann gonioprism. The arrow indicates the peripheral iris processes inserting on the anterior border-ring of Schwalbe.

exhibited a circumferential whitish line about 1 mm. inside the limbus.

Although accurate vision could not be determined because of the infant's age, good central fixation was present in each eye. The corneal light reflexes were centrally placed and therefore did not overlie the displaced pupillary openings. Both pupils reacted well to light.

Examination of the eyes under anesthesia was performed with use of a binocular microscope and a Goldmann gonioprism. The embryotoxon was noted to be a clear hyaline-like membrane on the posterior surface of the cornea that protruded into the anterior chamber. There were numerous adhesions across the chamber angle between the peripheral iris and this glass-like membrane in both eyes (Fig. 3). It was estimated that these adhesions occupied about 30% of the angle circumference in each eye. In the eye with the corectopic pupil, the peripheral iris adhesions were seen to be more prominent in the area toward which the pupil was displaced and appeared to be the factor causing the distortion of the pupil. In the eye with the slit-like pupil, the adhesions were very dense in an area immediately above and also directly below the pupil. It appeared that these dense membranes would not allow the pupil to contract down to a round shape and were responsible for the pupillary distortion.

The corneas measured 10 mm. in diameter, and the Schiøtz tension was 22 mm. Hg O. U. Both fundi were normal. On dilatation, both pupils assumed a round shape, since the distorting peripheral iris adhesions were negated by the mydriasis (Fig. 4).

The past history revealed that pregnancy and labor were normal in all respects. The child weighed 7 lb. at birth, and there was no family history of any similar eye disorders.

Fig. 4.—Both pupils assume a round shape during mydriasis. The apparent exotropia is due to Bell's phenomenon, since the child is under sedation.

Summary

This case is considered of interest because of the following aspects:

1. A prominent anterior border-ring of Schwalbe is associated with anomalous peripheral iris adhesions. These adhesions were responsible for the pupillary distortion, which was manifested by a slit-like pupil in the right eye and corectopia in the left eye.

2. On dilatation, the pupils became round, showing that the peripheral iris adhesions prevented the contracted pupils from assuming a normal round shape.

3. Glaucoma did not occur, since approximately 70% of each angle was open on gonioscopic examination.

4. On monocular fixation of a light, the light reflex was centrally placed on each cornea and therefore did not overlie the displaced pupils. There was no tendency for either eye to deviate into such a position that the light would pass in a straight line through the pupil to the macula. The reason for this fact is that displaced pupils do not induce either a phoria or a tropia if the eye has no significant refractive error. This is in accord with known optical principles.

5. There was no known familial history, whereas often there is a strong hereditary tendency.

Dr. J. Robert Fitzgerald gave help and advice in the examination of this patient.

U. S. Army Hospital, Camp Zama, APO 343, San Francisco.

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Ocular Myiasis Caused by Oestrus Ovis

B. N. PITTENGER, M.D., Paris, Ky.

On Nov. 2, 1957, a white man, aged 23, came to my office complaining of a feeling of foreign body or bodies in his right eye. He stated, "I removed what looked to me like three small worms as they crawled across the front of my eye."

On examination I found what appeared to be dipterous larvae similar to ones I had seen in a number of cases in Algeria during my Army duty in World War II. His only symptoms were lacrimation and a feeling of something moving across the globe. He had noticed his symptoms about three hours earlier, while washing his car. On inquiry he said that while he was washing his car a fly or other insect flew close to his eye but did not strike the eye. He stated that his eye had a sense of dampness but he did not associate that with the fly.

I applied local anesthetic tetracaine (Pontocaine), which was effective from his standpoint but had no effect on the larvae. The larvae were very adherent to the conjunctiva, and it was difficult to recover any of them until 5% cocaine was instilled; then they could be lifted off with ease. This was also my experience in North Africa. I removed nine larvae and preserved two under a cover glass for further investigation by the Department of Parasitology, University of Kentucky, Lexington, Ky.

The larvae were white and about 1 mm. long, with a suggestion of dark coloration at the head. They were difficult to see without a magnifing lens. In each case I have seen the larvae were deposited directly on the eye while the fly was in flight.

The eye was thoroughly irrigated, and as late as March 27, 1958, no additional symptoms have been noticed.

Submitted for publication Feb. 27, 1958.

My experience with ocular myiasis has been limited to my small experience in Algeria and the one instance in Kentucky. I saw no complications in any of these cases reported.

Mr. Elden G. Burcham, Department of Parasitology, University of Kentucky, Lexington, Ky., provided positive identification of these larvae, and I quote from his personal communication to me:

"Thank you for sending the fly larvae to me which you removed from the eye of one of your patients. Both specimens are unmistakably the sheep bot fly, *Oestrus Ovis*; the same species which you stated you saw in Africa. Both appear to be first stage larvae. The species is world wide in distribution and has been at least reported from sheep in Kentucky. I have not had an opportunity to examine the literature to determine if a case of ocular myiasis has ever been reported previously from Kentucky.

"A rather good reference on flies causing myiasis in man is 'The Flies that cause Myiasis in Man,' by Mauice T. James; Miscellaneous Publication, No. 631, U. S. Department of Agriculture, U. S. Government Printing Office, Washington, D. C.

"One French reference (Dupuy d' Uby 1931. A propos d'un nouveau cas de myiase oculaire a *Oestrus Ovis* observe a Alger. Inst. Pasteur d' Algerie, Arch. 9:630-637, illus.) gives some complete case histories, a symptomatology, and diagnosis."

Capt. Bernard D. Burks, Sn. C., of the Headquarters of the 10th Malaria Survey Unit in North Africa, identified the specimens I encountered overseas. I quote from his letter of July 7, 1943:

"The identification I made of the dipterous larvae which you removed from the eye of a patient on June 28 proves, on close study of the specimens, to be incorrect.

Rather than a *SARCOPHAGA*, the larvae are those of *Oestrus Ovis*, the nose bot of sheep."

Herms [1] reported a case of three larvae of this species being removed from the eye of a patient in Honolulu. The larvae were buried in the sclera and were extremely adherent to the conjunctiva, causing acute conjunctivitis, lacrimation, and ulceration. Herms is of the opinion that these larvae, which are normally deposited in the nasal passages, reached the eye by traveling up the nasal passage into the nasal sinuses and thence reached the eye via the lachrymal duct.

Strong,[2] however states that Oestrus Ovis has been known to deposit its larvae on the eyes or eyelids of shepherds in Algeria; similar infestations are said to be fairly common in South America.

Tassman [3] cites two cases of larval conjunctivitis due to Oestrus Ovis.

4 E. 4th St.

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Clinical Notes, New Instruments and Techniques

New Corneoscleral Suturing Forceps

W. C. THOMAS, M.D., Brunswick, Ga.

The great number of methods which have been suggested for closing wounds in the eyeball, traumatic or surgical, seems to indicate that the ideal method has not yet been devised. Preplaced sutures in surgery are favored by most surgeons, and there seems good reason for this. First, the coaptation margins of the wound are more apt to be fitted together without sliding or puckering with more strain on one side of the wound than the other. Second, the sutures are much easier to put in, since much more meticulous handling is necessary after the eyeball is opened. However, on the other hand, the untied sutures hamper the free movements of surgeons' and assistants' hands and become entangled with instruments. The risk of making accidental tension on the preplaced sutures, and the risk of snarling and kinking causes anxiety for the operating crew.

I am introducing the instrument here described as an aid in placing postincision sutures and in closing traumatic openings in the cornea or sclera. It is fashioned from a 4½ in. thumb forceps, the blades being altered to adapt it to this job. One blade has a plane surface with the terminal 3 mm. made 0.5 mm. thinner than the remainder, with an offset or step between the two portions, and the other has two light tines about 10 mm. long, about 0.5 mm. wide at the end, with about 1.5 mm. of space between them. The tines are slightly curved toward the opposite blade.

For purposes of description I will call the tined blade the upper blade and the plane blade, the lower, since this is the position of the blades with respect to the field of operation. At 3 mm. from the end the lower blade has a step or offset 0.5 mm. high; the surface of both portions is perfectly smooth. This blade is slightly narrower at the end than the over-all width of the tined blade at the end. The two tines of the upper blade are 0.5 mm. wide at the end, 1.5 mm. wide at the base, and 1.5 mm. apart. Each tine has a mark on the upper surface at a point just above the step in the lower blade. This gives the surgeon opportunity to be sure that the coaptation margin of the wound is resting against the offset in the lower blade. In suturing wounds of the cornea or sclera the margin of the incision is grasped in such a way that marginal surface rests against the step in the blade of the forceps. The upper blade will hold the cornea or sclera with very little pressure and a minimum of injury. The point of the needle is passed between the base of the tines and along the surface of the lower

Submitted for publication April 3, 1958.

The illustration shows the essential makeup of the instrument as described in the text.

blade to enter the margin surface of the incision half way between the intraocular and the extraocular surface. The point of the needle is then directed upward so as to emerge in the corneal surface the proper distance from the incision. If the double-armed suture is used, the second needle is placed in the opposite side in the same manner as described for the first. While the double-armed suture is possibly safer in closing incisions in the globe, some may prefer to use single-armed sutures.

With the single-needle suture the first side is approached by first placing the needle in the corneal surface between the terminal part of the tines and directing it toward the upper edge of the ledge in the lower blade. If the needle point strikes the ledge, the surgeon will know immediately that it must be partly withdrawn and directed so that the point will miss the step. The same needle is introduced on the opposite side in the same manner as described for the double-needle suture.

In the case of wounds made with blunt instruments the lips of the wounds may be crushed and irregular, in which case great care will be needed to see that the margin does not ride up onto the step. In the case of such a wound I have found the Liegard or Stallard suture to be preferable if the opening is 5 mm. or more long. This instrument is of great help in putting in this type of suture if it must be done after the eyeball is opened, as in the case of accidental injuries and when a preplaced suture is accidentally cut or taken out. The wound margin is grasped with the forceps just as in placing the sutures described above, and the needle is started in the corneal surface very close to the outer edge of the tine and directed under both tines the proper distance from the wound margin. In case it is desirable to take a smaller bite with the needle, a half-curved small needle can be easily brought out between the tines. After considerable experience in putting these sutures in dog and cat eyes I find that it is very easy to put them in without penetrating the full thickness of the cornea. However, with needles larger than the Kalt and similar corneal needles greater care is needed to avoid full-thickness bite.

In fact, it was not until after painstaking trials over a period of months that I decided that the Liegard suture has a definite place in eye surgery and possibly should be used in selected cases. This instrument has been a great help in my hands in experimental as well as operating-room cases.

1616 Reynolds St.

New Type of Enucleation Scissors

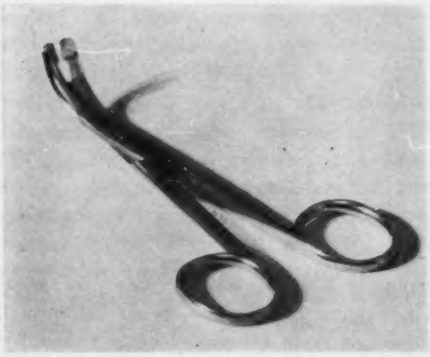
DON M. SMART, M.D., Dallas, Texas

It was believed that the present type of enucleation scissors could be improved by adding a notch in the blades for trapping the optic nerve. An attempt was made to use standard-type scissors and notch the blades. It was found that a sufficiently large notch would weaken the blades too much and that the blades would not be closed at the depth of the notch.

The new scissors have a slightly wider blade, to accommodate the notch and make complete closure. The notch was not rounded, in order make it easier to identify the optic nerve.

With these scissors the optic nerve can be identified by straddling the nerve with the blades and then withdrawing while pressing against the nerve with one blade; the nerve can be felt to cross the notch. The scissors are closed until the firmness of the nerve is felt; the nerve is thus trapped in the notch. The scissors can be brought against the back of the globe for orientation

Submitted for publication March 25, 1958.



Enucleation scissors with notched blades for trapping the optic nerve.

and then slid toward the apex of the orbit for the desired length of nerve. Hemostasis may be enhanced by exerting pressure on the nerve for a minute or so at less pressure than is required for cutting the nerve. When the cut is made, there is no possibility of partial severence of the nerve due to its slipping out of the ends of the blades. The notch is placed at such a distance from the tip of the blades that there is little danger of cutting Tenon's capsule with an overshoot of the free tip.

The enucleation scissors are manufactured by V. Mueller and Company, 320 S. Honore St., Chicago 12. The photograph was taken by Mr. Louis Pedigo.

219 Dallas East Medical Center, 9323 Garland Rd. (18).

Annual Reviews

Glaucoma, 1957-1958

BERNARD BECKER, M.D., St. Louis

I. Facility of Aqueous Outflow (C)
A. Measurement
B. Site and Nature of Resistance
C. Experimental Aspects
D. Clinical Aspects
1. Diagnosis
2. Therapy
II. Aqueous Formation (F)
A. Theory and Measurement
B. Alterations
1. Spontaneous and Neurogenic Changes
2. Carbonic Anhydrase Inhibition and Aqueous Flow
3. Other Alterations in Rate of Aqueous Secretion
III. Episcleral Venous Pressure (P_v)
IV. Miscellaneous Glaucoma Topics
A. Visual Fields and Optic Nerve
B. Glaucoma Detection

The present review attempts to discuss pertinent information added to the above categories in the literature of the past year. In addition, an effort is made to review critically selected aspects of the current status of the subject. The bibliography is confined to material available as of July, 1958, but excludes references incorporated in previous reviews.

I. Facility of Aqueous Outflow (C)

A. Measurement.—Further efforts are being directed toward discovering, evaluating, avoiding, and correcting for sources of error in the measurement of the outflow facility.[1,184,202,213,218,241,273,277,295,343,476,587,592,674,723,763,773] In addition to eye movements, patient tenseness resulting in lid squeezing, and the technical difficulties and inaccuracies of instrumentation in tonography, a host of other errors may arise. These stem from problems of calibration, variations from assumed average values for scleral rigidity and corneal curvature, changes in blood volume within the eye, alterations in episcleral venous pressure, possible changes in the secretory and outflow characteristics of the eye induced by the application of the tonometer, and other less well-recognized potential sources of error.

1. Tonometers: The Goldmann applanation tonometer is proving to be an accurate sensitive instrument, easily used in everyday office practice, and rugged enough to stand up under continuous use in a busy clinic.[277-279,421,529] Besides providing estimates of intraocular pressure essentially independent of scleral rigidity, the applanation measurement becomes a prerequisite to subsequent tonography in order to correct for variations from the assumed average rigidity coefficient.

The "friction-free" modification of the Schiøtz tonometer appears to incorporate valuable features for the more accurate measurement of ocular tension.[662] According to a recent detailed description, a constant indentation recording tonometer strapped to the patient's head permits considerable flexibility and presents opportunities for continuous tonometry during change of position, exercise, and other activities.[491] The high normal values for intraocular pressure with this instrument (av., 19 mm. Hg) as compared with the applanation (15.4 mm. Hg) and electronic tonometers (16.1 mm. Hg) suggest the need for further calibration studies of the new tonometer.

The dependence upon intraocular pressure of the vibration characteristics of the

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From the Department of Ophthalmology, Washington University School of Medicine and the Oscar Johnson Institute.

eye and the associated subjective phenomena offer new approaches to the estimation of intraocular pressure.[241]

2. Calibration Tables: In spite of criticism and probable future changes, the 1955 Friedenwald tables are proving most consistent, not only within themselves but also in comparison with applanation measurements.[376,401,421,520,521,626] In addition, when tonographic tracings are interpreted with these tables, the facilities of outflow so determined are in excellent agreement with perfusion values on the same eyes. The use of perfusion methods in vivo are of particular significance in this regard. Any future modifications of current tables should rest upon data obtained on human eyes in vivo.

3. Size of Tonometer Footplate Hole: A more careful evaluation of this previously unrecognized source of error in tonometry and tonography has led to the important practical conclusion that the present electronic tonometers should not be depended upon for accurate determinations at scale readings less than "four." * [522] At lower scale readings intraocular pressure is overestimated, scleral rigidity readings are false, and outflow facility and rate of flow are often falsely interpreted as hypersecretion. The use of correction factors or a heavier weight reveals the true status. Most mechanical instruments are valid down to scale "three." Efforts directed toward reducing and standardizing the size of the footplate hole are in progress.

4. Ocular Blood Volume: Within the limits of error of the ingenious methods used, tonographic alterations in intraocular pressure do not appear to alter the blood content of the posterior segment of the cat eye.[85-88] Although this is reassuring, the possibility of small blood-volume changes during tonography in some human eyes remains an important potential source of error. This is true because even relatively small percentage changes in total ocular blood volume could represent large fractions of the relatively small volume of fluid expressed from the globe during tonography. Further studies with labeled red cells and other techniques are needed.[137,246,269,275,346,397,469,748,749,801,802]

5. Scleral Rigidity: There is additional evidence that the scleral rigidity coefficient itself, as defined by Friedenwald, may not remain constant at different pressures in enucleated animal and human eyes.[348,375,469-471,494,573,574] However, in living human eyes, the present calibration data for the Schiøtz tonometer are self-consistent and provide excellent linear plots of log P vs. $\triangle V$. Furthermore, the lines so obtained extrapolate back to P_o values in good agreement with applanation readings.[67,278,521] Recently, by increasing the area of applanation, independent estimates of the relation between intraocular pressure and corneal indentation volume have been reported.[523] The values obtained in this fashion also fall on the same approximately straight line on a semilog plot for the individual living human eye. Furthermore, corrected tonographic estimates of outflow facility agree well with measurements on the same eyes by methods independent of scleral rigidity, such as constant-pressure tonography or perfusion in vivo or in vitro.

The discrepancies between the clinical scleral rigidity data and the studies on enucleated eyes may stem from the known post mortem changes that occur in the sclera and cornea. Additional discrepancies may arise from the methods of cannulation of enucleated eyes (e. g., alterations in anterior chamber depth),[353] uncertainties in extrapolation of pressure curves following sudden volume changes, the use of "artificial orbits" in vitro, and the possible use of nonstandard tonometers.

Clinical estimates of scleral rigidity continue to reveal patients with abnormal values for this coefficient.[63,278,328,422,661,788] Of great practical significance in glaucoma diagnosis are those eyes with low scleral rigidity, such as are seen in some patients with myopia [278,422,580,775] and in several

* Moses, R. A.: Unpublished observations, 1958.

instances of thyrotropic exophthalmos.†[774] It is in these groups that the diagnosis of glaucoma is easily missed by Schiøtz tonometry but readily discovered by applanation readings. In spite of the normal Schiøtz scale readings, however, the diagnosis in these eyes may also be suggested by flat tonographic tracings.

Of theoretical as well as clinical interest is the recent evidence that water drinking often reduces the measured scleral rigidity coefficient.[362] This tends to produce falsely low estimates of both intraocular pressure and outflow facility. It accounts in part for better recognition of glaucoma by flattening of the tonographic tracing than by elevation of the Schiøtz tonometric values following the water-provocative test.

Another practical aspect of scleral rigidity in the management of glaucoma is the lowering of this coefficient for a variable period in some glaucomatous eyes following certain miotics or some types of surgical therapy. This results in Schiøtz data which provide false assurance of adequate pressure control. The true status is suggested by flat tonographic tracings and recognized readily by elevated applanation readings.

The fact that scleral rigidity can be varied in the individual eye presents an exciting tool for clinical and animal research. Studies of the intimate physical, histologic, and biochemical alterations induced by hydration, enzymes and their inhibitors, hormonal and nutritional imbalances, and neurovascular phenomena may provide considerable insight into the problem of what constitutes the scleral rigidity itself. In addition, they may provide basic information as to the nature of myopic and thyrotropic ocular disorders.

6. Episcleral Venous Pressure (P_v): An average constant correction factor of 1.25 mm. Hg for the increase in P_v during tonography has been incorporated in the present tables. However, there is new evidence to indicate that, if measurements are made in aqueous veins rather than episcleral vessels, this value may not be valid for all eyes. Particularly for tonography in the normal eye, somewhat higher correction factors (7 to 8 mm. Hg) may be more appropriate.[277,278] In fact a linear relationship has been demonstrated between the elevation of pressure in the eye in the aqueous veins when the eye is compressed. The aqueous vein pressure varies less with intraocular pressure in glaucomatous eyes, however. Ideally, therefore, the magnitude of the correction factor should be computed for each eye by separate measurements of P_v during tonography. The application of the appropriate correction would tend to increase the outflow facility value calculated for many normal eyes and to alter the estimate of the coefficient much less in eyes with glaucoma. The normal and glaucoma populations would then be separated more discretely.

7. Miscellaneous: An important possible correction factor in tonography may be the expression of fluid from the area of cornea subjected to the weight of the tonometer, especially the area under the plunger.[277,279,750] The volume expressed or distorted by this corneal plasticity would be interpreted falsely as anterior chamber aqueous humor lost and thus result in overestimates of outflow facility. Methods are needed for the estimation and correction of this possible source of error.

Various alterations in technique[72,339,579,694,695,715] are suggested, as well as attempts to use different parts of the tonographic curve for the calculation.[443,444,451] These modifications rarely improve the estimate of true outflow facility as compared with conventional methods.[55,67,295] "To suppress a part of a curve you must know this curve and its origin exactly, otherwise your amputation becomes arbitrary and influenced by wishes."[278] Although the beginning of the tracing may be subject to artifacts and errors, these are not corrected by omitting this part of the tonogram. The use of the tail of the curve decreases the accuracy of the measurement because of the compression of the tonometer scale (and the de-

† Gay, A. J., and Becker, B.: Unpublished observations, 1957.

creased magnification by many recorders) at greater indentation values. In addition, the difference is decreased (and less accurately measured) between the induced tonometric pressure (P_t) and the undisturbed intraocular pressure (P_o). Further errors result when straight line extrapolations are substituted for the true shape of the individual tonographic curve. In some reported instances the calculations used and conclusions reached with use of the end of the tracing are in error because of a disregard for the preceding events in the eye or a failure to utilize the true value for the initial undisturbed intraocular pressure (P_o). Similarly, tables or graphs designed for estimating outflow facility from the scale readings at times zero and four minutes do not give meaningful values for outflow facility when used for later parts of the tonographic tracing.[443,444,449,451] Another common error is the acceptance of the falsely high estimates of P_o derived from scale readings less than four (paragraph above on tonometer footplate hole) when using the beginning of the tracing. Thus, a variety of errors may result in much higher apparent facilities being found for the first part of the tonogram than for other segments. When suitable care is taken to avoid such errors, and especially if extreme caution is observed so as to obtain tonograms free of artifacts, similar facility values are found for all parts of the tracing in most eyes. This is even true if tonography is continued for as long as 20 to 30 minutes.[722]

B. Site and Nature of Resistance.—Studies continue on the structure and function of the normal and pathologic trabecular meshwork and outflow channels.‡[26,28,57,80,112,143,200,349,385,389,409,410,417,474,484,497,498,534,629,634,649,730,738,816] Our knowledge of the detailed structure of the normal human tabecular fibers is advanced by recent outstanding accomplishments with the electron microscope.§[259,260] Additional careful studies are anxiously awaited.

Dissections of the trabecular meshwork in perfused normal eyes demonstrate that 75% of the resistance is located between the anterior chamber and Schlemm's canal.[295] This modified experimental approach clarifies the situation and provides data which are in excellent agreement with other techniques previously reported.[61] Interestingly enough, removal of the entire trabecular meshwork eliminates the alteration of outflow facility with depth of the anterior chamber in the perfused enucleated human eye.[295]

Water-soluble "mucopolysaccharides" may be present in the trabecular meshwork of the living eye in very much greater concentration than previously suspected from studies of fixed and washed tissues. These can be demonstrated by iron-binding in vivo and subsequent staining.‖ It is hoped that such mucoid-like components may be made opaque to the electron microscope by chelating iron or other heavy metals so that their exact localization can be better appreciated. The site of formation, nature, and alterations of trabecular mucoids remain exciting problems. The changes in affinity for iron of the polysaccharides in glaucomatous eyes bring these laboratory studies very close indeed to the clinical problems of the glaucomatous disorders. The metabolism, enzymatic activity, and function of the cells of the trabecular meshwork and their relation to the corneal endothelial cells provide fascinating speculation.[78,138,799] Tissue culture and histochemical techniques may help in the resolution of these questions.[51,106-108,133,140,153-155,158,359,418,419,658,713,803,817]

In eyes with chronic simple glaucoma, pathologic changes are noted in the trabec-

‡ Flocks, M., and Brugge, E. H.: Studies of the Trabecular Meshwork of Normal and Glaucomatous Eyes, Exhibit, 107th Annual Meeting of the American Medical Association, San Francisco, June, 1958.

§ Garron, L. K.; Hogan, M. J.; McEwen, W. K., and Feeney, M. L.: Electron Microscopy of Ocular Tissue, Exhibit, 107th Annual Meeting of the American Medical Association, San Francisco, June, 1958.

‖ Cibis, P. A., and Yamashita, T.: Unpublished observations, 1957.

ular meshwork and are particularly well demonstrated in tangential sections.¶ [38,228,276,394,410,729,746] The suggestion has been made that the increase in intraocular pressure itself may further damage the trabeculae.[228] Interestingly enough, some instances of hypersecretion glaucoma appear to go on to develop impaired outflow facility after several years.[67] However, it is a common experience to see the outflow defect of very early glaucoma progress even when intraocular pressure is maintained at low levels by various intensive therapeutic means. Therefore, the elevated intraocular pressure would not appear to be the sole cause of trabecular damage. In fact, much evidence would favor the intraocular pressure rise as a relatively late consequence of the obstructed outflow in most glaucomatous eyes.

The gonioscopic classification of glaucoma continues to receive widespread acceptance.[193,593,710] It is hoped that, in addition to the recognition of pretrabecular resistance sites, one may begin to distinguish clinically the various subdivisions of trabecular and post-trabecular factors for more precise classification of the disease.

C. Experimental Aspects.—Attempts to decrease the outflow facility permanently have been largely unsuccessful.# [446,657,685,689,804,805] The reported effects of poppy alkaloids and citral on outflow channels and intraocular pressure [311,686] fail to find confirmation in other laboratories using tonometric, histologic, tonographic, and perfusion methods.* [79] Efforts directed toward successful breeding of animals presenting primary glaucoma are still in progress.

Decreases in outflow facility in the human eye are reported to occur during periods of stress or following topical levarterenol (*l*-norepinephrine).[374] As reported previously, decreases in outflow facility are also noted after spontaneous or induced partial suppression of the rate of aqueous formation in normal human and rabbit eyes.[55,62,223,415,451,597] On the other hand, glaucomatous eyes do not demonstrate this flexibility of outflow facility. The alterations in outflow resistance following carbonic anhydrase inhibition in normal rabbits can be prevented or reversed by aldosterone or fludrocortisone administration. Cervical sympathectomy in rabbits also results in some loss of the ability to decrease outflow facility when inflow is depressed.[62,347] Interestingly, the decreased secretory rate in alloxan-diabetic rabbits is not accompanied by reductions in outflow facility unless insulin is administered.[156] Thus in these acidotic diabetic rabbits with impaired secretion of aqueous, insulin restores intraocular pressure by decreasing outflow facility. All possible approaches to the important experimental decreases in outflow facility require further careful evaluation by tonographic and perfusion techniques, as well as by histologic and chemical studies.

In addition to the effects of hyaluronidase reviewed last year, many of the methods for increasing outflow facility in normal eyes described at the end of the 19th century are demonstrated again. In some species miotics, accommodation, increase in anterior chamber depth, or sudden alterations in intraocular pressure are found to increase the facility of outflow.[34,238,354,468] Care must be exercised in the interpretation of tonograms not carried out under steady-state conditions. For example, if a subject begins to accommodate just before the onset of the tracing and continues this act so that it lowers intraocular pressure during the tonography procedure, the change in scale reading may be superimposed upon the effects of the tonometer. The steeper tonogram so obtained may be falsely interpreted as a significant increase in outflow facility.[34]

Preliminary reports of an elegant study of the role of the parasympathetics in the control of intraocular pressure in the cat already provide data of considerable in-

¶ Flocks, M., and Brugge, E. H.: Studies of the Trabecular Meshwork of Normal and Glaucomatous Eyes, Exhibit, 107th Annual Meeting of the American Medical Association, San Francisco, June, 1958.

Hahn, K. A., and Becker, B.: Unpublished observations, 1957.

* Moor, W. A.: Unpublished observations, 1956.

terest.[33] Stimulation of the ciliary ganglion in this species produces contraction of the ciliary muscle in such fashion as to increase the depth of the chamber angle. It also appears to lead to an increase in the outflow facility as measured by perfusion. In addition, such stimulation produces rapid reductions in intraocular pressure, probably largely on a vascular basis.

D. Clinical Aspects.—Enthusiastic reports continue to appear as to the value of tonography as an adjunct to other methods in the diagnosis and evaluation of the therapy of glaucoma.[18,29,42,46,53,63,67,71,74,104,189,243,295,355,357,393,443,444,458,503,504,558,578,607,624,627,638,709,710,720,742,757,788] An excellent review and interesting discussion on tonography is presented in the Transactions of the Third Conference on Glaucoma sponsored by the Josiah Macy, Jr. Foundation.[538]

1. Diagnosis: A decrease in outflow facility with age may be demonstrated in animal and human eyes by perfusion and tonographic methods, as well as by estimates from turnover studies.[66] Interestingly enough, the outflow impairment is associated with a decrease in secretory activity, and so the intraocular pressure in normal eyes does not vary much with age.

As reviewed above, decreases in outflow facility follow various induced and spontaneous suppressions of aqueous formation in normal eyes. However, in the case of the aging population, reduced secretory activity as the cause of the outflow facility alterations is not established. In fact histologic changes are seen in the trabecula of many "normal" eyes of older persons and correlate with in vitro perfusion values.[410,629] In addition, a part of the recorded decline in outflow facility with age may be a consequence of the progressive decrease in anterior chamber depth.[693,729] It may even be hypothesized that the secretory reduction is in response to the outflow impairment. In these terms, glaucoma may be defined as a failure to decrease secretion in proportion to the decline in outflow facility or as an excessive decrease in outflow facility for a given secretory rate.

It is evident that the lower the outflow facility the greater the variation in intraocular pressure with secretory rate and the higher the intraocular pressure at a given rate of aqueous formation. Even in eyes with established glaucoma, the decline in secretion observed with increasing age may lower intraocular pressure in spite of the outflow disorder. This hyposecretion accounts for some of the difficulties in glaucoma detection but, on the other hand, also tends to avoid progression of the field defects.

A study of the families of patients with chronic simple glaucoma reveals, in addition to the previously described high incidence of unrecognized glaucoma, an amazingly frequent occurrence of impaired outflow facility.[67,364,650,710,711] This occurs even in the younger members of the family. Following the progression of the disorder in these selected cases should provide valuable information as to the life history of the disease and methods for its detection.

The use of tonography in association with gonioscopy and suitable provocative tests permits the earliest detection of the glaucomas.[16,37,59,63,67,70,116,193,287,288,396,443,489,561,618,624,631,633,653,679,694,708,754,758,776] Further experience with the mydriatic test in angle-closure glaucoma demonstrates its ability to recognize this disease in some 85% to 90% of eyes if tonography measurements are made.[70] Similarly, a P_o:C ratio over 100 after water-drinking characterizes over 95% of eyes with proven chronic simple glaucoma. The rare instances of combined forms of primary glaucoma remain sources of confusion.

Although methods of recognizing established glaucoma are well documented, data are sorely needed on the significance of the abnormal findings in otherwise apparently healthy eyes; in particular, the clinical interpretation of outflow impairment in the absence of pressure elevations needs further elucidation. At present the safest working hypothesis is to consider such eyes as suspiciously glaucomatous to follow them closely for pressure elevations.

One cannot judge the value of a method for the detection of early glaucoma on the basis of its identifying a large fraction of the population studied.[443] Information as to the value of testing methods can only be acquired by long-term follow-up of patients presenting the suspicious findings. Some three-year data are available which suggest the predictive value of tonography after water-drinking.[67] Thus a series of 40 normotensive eyes with no abnormalities except for a P_0:C ratio after water of greater than 100 were followed closely and reviewed after three years: 10 eyes (25%) demonstrated significant spontaneous pressure elevations (over 24 mm. Hg); 12 eyes (30%) developed decreased outflow facilities (less than 0.15), and 3 eyes lost visual field (Bjerrum scotomata). These preliminary studies need verification and longer follow-up periods.

Case reports and reviews appear on congenital,[18,96,102,144,163,187,257,263,290,306,307,368,412,462,482,485,546,552,568,619,665,696,705,706,725,776,777,791] angle-closure,[93,94,152,261,274,425,427,555,591,608,687,690,721,728,739] chronic simple,[152,425,456,481,544,560,680] and various varieties of secondary glaucoma.[2,22,90,121,136,145,188,222,225,250,265,291,331,336,341,428,434,439,440,480,536,540,551,557,559,571,576,605,625,637,656,664,681,710,731,745] The importance of preexisting chronic simple glaucoma in the pathogenesis of the vein occlusions in patients who develop hemorrhagic glaucoma is again emphasized.[63,123,208,414,531,753] The finding of a vein occlusion should lead to exhaustive studies for evidence of chronic simple glaucoma in both the involved and contralateral eye.

2. Therapy: (*a*) Miotics.[73,308,309,386,442,459,487,499,517,558,590,709,757,785,808] The search continues for more effective miotic agents with fewer side-effects, including anticholinesterase compounds as well as direct parasympathomimetic drugs.[289,293,294,367,431,508,598,652]

Further studies with the newer potent long-acting inhibitors of cholinesterase continue to demonstrate their value in the therapy of chronic simple and secondary glaucomas. Echothiophate (Phospholine) iodide and decamethylene bis-(m-dimethylaminophenyl N-methyl-carbamate) dimethobromide (BC 48) are water-soluble and stable compounds which lower intraocular pressure in normal and glaucomatous eyes. In both instances, this is accomplished by significant increases in outflow facility.[289,431,508,598]

Repeated tonography demonstrated a 68% average increase in outflow facility in a series of 15 normal eyes following topical echothiophate.[598] Of particular importance clinically was the finding of significant improvement in the outflow impairment in some 70% and adequate pressure control (20 mm. Hg or less) in approximately 50% of a group of 106 eyes with chronic glaucoma uncontrolled on other medical therapy. This was achieved by the addition of echothiophate 0.25% once daily or once every other day to the previous medical regimen. Similar results have been obtained with 0.5% BC 48 applied once every one to three days.

Although side-effects such as brow pain and headache are common after the first few applications of echothiophate, they are usually controlled by salicylates. Most patients do not experience such symptoms after the first few days on continued therapy. However, occasional patients experience diarrhea, and children often demonstrate iris cysts on continued administration. Most disturbing has been the appearance of a fibrinous iritis in three patients with chronic simple glaucoma after three to five days of echothiophate therapy. When therapy was stopped, this subsided very slowly in spite of topical steroids, mydriatics, and subconjunctival administration of pyridine-2-aldoxime methiodide (P_2AM). In two instances dense posterior synechias formed.

Pyridine-2-aldoxime methiodide reverses the systemic and ocular effects of BC 48 and echothiophate.[303,304] When injected subconjunctivally it permits the reversion of the pupil size and outflow facility to pretreat-

ment levels.† The long-term uses of echothiophate, BC 48, and related agents are being explored further in several clinics. Like isofluorophate (DFP), the use of these agents is probably contraindicated in eyes with narrow angles.

In a review of the prognosis of 250 eyes with unoperated chronic simple glaucoma treated with miotics alone, an initial intraocular pressure on therapy of 24 mm. Hg or less resulted in continued successful therapy for three years in only about one-half of such eyes.[64,67] On the other hand, pressure levels of 20 mm. Hg or less assured control for this period of time in approximately three-fourths of the series. Tonographic studies in these same eyes provided data permitting more accurate prognostication. One of the best means of anticipating the status of control over the three-year period was the ratio P_o:C. Thus an initial P_o:C value on miotic therapy of less than 100 predicted successful control in over 90% of such eyes.

(*b*) Surgery. In angle-closure glaucoma, tonography and gonioscopy complement one another in the decision as to whether to perform an iridectomy or a filtering operation.[70,678] An adequate outflow facility (over 0.15) under medical therapy assures one of successful control by peripheral iridectomy plus miotics in almost all instances (only 1 failure in 71 eyes). On the other hand, eyes with an outflow facility less than 0.10 have a 77% failure rate following peripheral iridectomy. The iridencleisis operation, however, has a failure rate of approximately 20% regardless of preoperative outflow facility. It would thus seem wise to reserve iridencleisis or other filtering procedures for those angle-closure eyes with markedly impaired outflow facility (less than 0.10) which do not improve and are not controlled following peripheral iridectomy.

The reported failure of progression of essential iris atrophy after a broad iridectomy needs confirmation. It presents exciting possibilities for the arrest of this troublesome disease process.[166]

Again this year the literature abounds with enthusiastic reports of revisions and modifications of filtering procedures and more sober reports of the complications of previously described techniques.[4,5,24,36,46,52,56,73,75,77,83,84,91,127,135,162,175,176,183,211,219,240,247,280,283,305,310,333,366,370,381,383,398,400,420,426,460,496,500,512,513,527,541,545,547,554,569,570,596,604,622,636,642,643,647,651,654,655,700,701,704,707,710,716,726,727,733,736,743,752,757,759,760,782,808,815,818] Further histologic studies on the mechanism by which filtering procedures function and the possible role of constituents of the aqueous humor may lead to new approaches to these problems.‡ [161,357,429,641,724]

The general trend continues in the direction of conservative or medical management of the glaucomas with open angles, unless surgery becomes mandatory because of progressive field loss. This conservatism stems not only from the disappointing results and complications of surgery but also from the availability of more effective agents acting both on the outflow disorder and on the rate of aqueous formation.

II. Aqueous Formation

A. Theory and Measurement.—The intimate details of the mechanism of secretion of aqueous humor remain obscure.[100] The Friedenwald redox pump hypothesis is subject to criticism on the basis of the stoichiometric relationships demanded by the original formulation.[54] Inadequate oxygen is consumed by all ciliary processes of the rabbit eye to account for the postulated hydroxyl ions formed. Furthermore, the theory needs suitable modifications to explain the hydrogen and chloride ion excesses in the human and monkey eye rather than the bicarbonate excess and hydrogen ion deficit of the guinea pig and rabbit eye.[62] In addition, in contrast to the rabbit and guinea pig eye, recent findings on human

† Leopold, I. H.: Personal communication to the author; Drews, R. C., and Becker, B.: Unpublished observations, 1958.

‡ Teng, C. C.; Chi, H. H., and Katzin, H. N.: Histology and Mechanism of Filtering Operations, Exhibit, 107th Annual Meeting of the American Medical Association, San Francisco, June, 1958.

aqueous humor suggest a greater sodium deficit than expected on the basis of the Donnan equilibrium.[118]

Modifications and mechanisms for secretion are proposed which involve the secretion of only the excess over plasma of a particular ion, the recycling of electrons, the postulation of anion or cation carriers, or the direct supply from carbon dioxide of the hydrogen or bicarbonate ions for secretion or ion exchange.[65,415] Similar speculation pervades the large body of literature on secretory activity of cells in many locations.[81,142,147,164,170,171,190,191,209,221,325,326,329,340,477-479,505,699,781,819]

The energy for most proposed transfer mechansims is believed to be derived from oxidative phosphorylation.[688] There is evidence that this energy source is also essential for aqueous humor formation.[54,101,766]

In such secretory sites as the renal tubule, choroid plexus, and ciliary body, interest in pinocytosis (cell-drinking) [441] as a transport mechanism has been reawakened by recent electron-microscopic findings.[76,342,572] In the ciliary epithelium, infoldings of the cell membrane on the posterior chamber side extend deeply into the cell and the cell contains numerous vesicles.[342,563,691,793] One may speculate that environmental fluid is pinched off and transported across the cell in these vesicles. During its transit it is suitably modified by secretory and diffusional processes to form the aqueous humor.

Pinocytosis as a transport mechanism in the ciliary epithelium finds support from studies with carbonic anhydrase inhibitors. Such agents increase the number of vesicles seen, perhaps by slowing down the rate of transport of the vesicle.[57,342] In addition, in the rabbit, carbonic anhydrase inhibition results in little alteration of measured osmotic excess of aqueous humor over plasma.[58,179,435,436,719] Furthermore, questions have been raised as to the presence of an osmotic excess in the aqueous in vivo [415,435] and experimental evidence has been presented to indicate that the rate of flow of aqueous humor in the cat is not as dependent upon osmotic factors as was suspected.[57,58] The role of pinocytosis in explaining these and other findings needs elucidation.

Further studies are in progress as to the effects of various agents as well as alterations in intraocular pressure itself on the appearance of the ciliary epithelium and other intraocular structures as viewed directly in vivo, by conventional histology, and by the electron microscope.[115,148,259,302,473,488,691,793] The description of decreases in the infoldings of the cell surface, alterations in mitochondria and vesiculation, and other changes need further elaboration as to specificity, mechanism, and significance.[342,563,691]

Reviews and studies of posterior chamber and vitreous dynamics continue to amplify our understanding of the correction factors to be applied in the evaluation and interpretation of anterior chamber turnover data.[65,214,298,301,379,490] In addition, such studies serve to increase our basic understanding of the nature of the primary secretory product. However, the currently accepted mathematical theories are not dependent upon any one proposed mechanism for aqueous secretion or any particular product secreted. Similar detailed data and formulations are needed for the effects of corneal- and lens-transfer mechanisms and metabolism on anterior chamber dynamics.[149,210]

The external recording of radiations from the eye after systemic or intracameral injection of a radioactive isotope has been considered repeatedly as a direct means of measurement of the rate of transfer out of the individual eye (k_o). Unfortunately such experiments suffer from the errors of recording unduly from the cornea because of its proximity to the counter. This may be avoided in the intracameral approach by measuring the rising plasma concentration rather than counting the loss of radioactivity directly from the eye. However, the measurement still incorporates the alterations and reactions of the eye to the intracameral injection itself. For example, in cannulation experiments in vivo, it is common to induce almost complete cessation of

secretion in the rabbit eye. When radioactive sodium is injected into the anterior chamber of rabbit eyes and k_o estimated from the slope of semilog plots of the rising plasma radioactivity levels (log $[C_{p_\infty}-C_p]$ vs. time), average values as low as 1% per minute are obtained. This may represent the total k_o for the normal eye, but it appears more likely to represent partial or complete secretory suppression and thus a closer estimate of k_d, the rate of loss from the anterior chamber by diffusional exchange with plasma.

An ingenious new approach to this problem is the injection of labeled substances into the vitreous of the rabbit eye.[490,492] Here its turnover is so much slower that the eye may have the opportunity to recover from the trauma of injection before much of the substance has left the eye. When Na^{24} is injected, average values are obtained for the rate of loss from the vitreous of the individual eye (0.156% per minute) [490] which are in very close agreement with previous estimates of mean accumulation rates in the vitreous after intraperitoneal injections (0.155% per minute).[244] When larger molecules are used, such as serum albumin, the rate of loss from the vitreous may be confined to that part leaving with the aqueous humor from the anterior chamber.[492] In this special circumstance, with assumptions as to relative volumes of various chambers and measurements of the steady-state ratio of concentration in anterior chamber to that of the vitreous, estimates of k_o for the individual eye may be obtained. The preliminary studies of this method demonstrate values for k_o as low as about 1% per minute. The method requires further evaluation as to the normality of the rate of flow in the eye into which sodium has been injected, the possible influence upon the measured vitreous decay curve of accumulation of the radioactive label in the cornea or lens, the variations among animals, and the possibility of other sources of error.[39,109,110]

A number of studies confirm and amplify the previously reported aqueous humor chemistries of animal and human eyes.[26,141,146,286,301,323,361,615,807] In addition, aqueous humor proteins and amino acids are being studied by ingenious microelectrophoretic and other methods.[90,100,101,115,194,236,237,266,267,324,388,516,528,530,613,702]

Continued efforts to use short cuts for the laborious detailed turnover studies with fluorescein are often difficult to interpret. Thus, the fluorescein appearance time when done under carefully controlled conditions may provide a rough relative estimate of the rate of aqueous flow in a single eye.[453] However, the shape and height of the curve for anterior chamber fluorescein concentration at various times after injection cannot be translated into statements about aqueous flow.[21,185,586,645] Even at best, in addition to the rate of aqueous flow, this method measures the over-all picture of at least such variables as changes in plasma concentration and protein-binding of fluorescein, posterior chamber concentrations, diffusional exchanges and permeability alterations, and anatomic variations of the individual eye. For interpretation, simultaneously obtained continuous plasma-concentration curves (and posterior chamber values) are needed.

B. Alterations in the Rate of Aqueous Secretion.—Among a wide variety of theoretical possibilities, transfer mechanisms can be altered by affecting membrane permeability characteristics, by interfering with or altering the supply of secretory products or metabolites to the cell, by changing the environment about or within the cell, by affecting enzymatic metabolism of the secretory cell itself, or by altering the rate of movement of vesicles or other transport vehicles.[27,82,170,190,191,325,416,424,478,479,542,565,566,640,688] For example, several of these factors are considered in studies on the mode of action of insulin.[416,565,635,673,814] The methodology is needed for evaluating more of these possible effects upon the secretion of aqueous humor.

1. Spontaneous and Neurogenic Changes: A significant decline in secretory rate after

the age of 60 years is recorded by tonography in both normal and glaucomatous human eyes.[66] This is consistent with turnover studies and with the histologic appearance of the ciliary body. As indicated above, the decrease in secretion provides a mechanism whereby intraocular pressure in "normal" eyes is maintained reasonably constant throughout life. Spontaneous hyposecretion may explain the absence of elevation of intraocular pressure and damage to the optic nerve in spite of a decrease in outflow facility.[66,277] It also affords a physiologic basis for pharmacologic and surgical efforts to control intraocular pressure by decreasing the rate of aqueous formation. Speculatively it is of interest that the decline in secretory rate with age is associated with a decrease in anterior chamber volume.[693,729] Thus constancy of composition of aqueous humor tends to be maintained in the aging human eye, just as in different-sized eyes of various species.

At a given outflow facility, the secretory rate regulates the intraocular pressure and its fluctuations and is an important factor in determining the amount of glaucomatous damage to the optic nerve. With the high incidence of outflow abnormalities, the control of secretory rate needs further elucidation. Of great value in such studies would be more information as to ocular, endocrine, vascular, and neurogenic mechanisms of "spontaneous" alterations in secretory rate.

Studies of diurnal variations, consensual reactions, the effects of the administration of various agents, the consequences of the excision of endocrine glands or the administration of their hormones, and the effects of stimulation and ablation of various parts of the nervous system offer promising approaches to these important problems. Much of the available information in this complex field has been summarized recently.[573]

Diurnal variations in intraocular pressure appear to be a consequence of changes in secretory activity.[223] The magnitude of the pressure change induced is dependent upon the outflow facility. In glaucomatous eyes, even small variations in rate of aqueous formation result in large fluctuations in intraocular pressure. In normal eyes, the pressure changes are much less and are further minimized by compensatory alterations in outflow facility.[55,452]

Consensual eye reactions involve apparent alterations in secretory activity which are easily studied. Thus the tonographic procedure on one eye induces a fall in intraocular pressure in the opposite eye without changing outflow facility.[703,709] Retrobulbar anesthesia blocks the reaction when injected behind the stimulated eye but not when administered behind the contralateral eye.[573,609] The previously reported prevention of this "ophthalmotonic consensual reflex" by ganglionic blocking agents is not verified in all laboratories.[451,724] It would appear that consensual reactions result from vascular and possible humoral[100] factors in addition to the neurogenic aspects of the response.

The finding of identical fluorescein appearance times in both eyes of a rabbit after one eye has been subjected to tonography is of considerable interest.[181] It is concluded by the author to indicate "no significant change in the rate of aqueous formation" following tonography. An equally appealing interpretation, which is still consistent with the data, would be that aqueous flow is affected similarly in both eyes following tonography on one eye.

Contralateral elevations and depressions of intraocular pressure have also been noted inconstantly following thermal irritation, trauma, anterior chamber punctures, vortex vein ligation, glaucoma surgery, etc.[365,438,573,610] Alterations in some of the contralateral responses are reported to follow the administration of topical and systemic agents.[609]

The recording of the electrical discharge from the posterior ciliary nerves of cats and monkeys offers new opportunities for studying the sensory aspects of alterations in intraocular pressure.[573,764,765] It permits the study of the role of pressor receptors in the eye in the control of its own secretory ac-

tivity as well as their role in effects on the opposite eye. In addition, the responses and alterations induced by various neurogenic, pharmacologic, and vascular influences can be explored.

The literature during the past year on central nervous system control of intraocular pressure offers little additional information beyond that reviewed last year.[8,9,10,11,12,13,14,33,49,50,167,206,207,213,215,233,248,271,356,374,403,404,405,461,532,533,599,601,602,660,717] There can be little doubt of centrally innervated neurogenic, neuromuscular, neurovascular, and neuroendocrine influences upon intraocular pressure. However, sound experimental data are lacking on the modes of action of such factors on the eye. Short-term effects may result from changes in ocular blood volume, but the more persistent changes must be resolved into temporary or permanent alterations in outflow facility, episcleral venous pressure, or rate of aqueous formation.

Cervical ganglionectomy has again been demonstrated to decrease temporarily the rate of formation of aqueous humor.[447] Interestingly enough, stimulation of the preganglionic cervical sympathetic causes a decrease in aqueous secretion.[415] Furthermore, although preganglionic sympathotomy is without effect on intraocular pressure,[454] it prevents the homolateral fall in intraocular pressure induced by diencephalic stimulation.[271,272]

Many observers consider neurogenic or circulating factors of significance in the acute angle-closure glaucomas as well as in the rare instances of hypersecretion glaucoma. Their role in chronic simple and other glaucomas remains speculative.[3,134,205,216,264,351,380,467,564,644,676,677,732,741,751,779,780] Reports also appear on use of vitamins, sedatives, tranquilizers, sleep, and psychotherapy in the treatment of glaucoma.[6,32,40,97,315,330,392,445,501,502,550,600,646,780] Although of considerable theoretical and practical interest, their effectiveness and mode of action remain obscure.[220] There is a need for studies of carefully followed glaucoma patients treated with these agents, with use of adequate controls and preferably the "double-blind" technique.

2. Carbonic Anhydrase Inhibition and Aqueous Flow: The short-term and long-term uses of acetazolamide, as well as its limitations and abuses, are now well established and are much as outlined in previous years.[3,7,15,37,65,92,98,113,124,157,177,178,182,204,229,249,294,360,386,399,402,442,451,457,487,499,514,517,562,587,597,611,620,627,667,710,718,734,740,744,757,762,785,789,808] Interest is increasing in the development and study of newer carbonic anhydrase inhibitors.[68,150,230,282,285,296,297,318,338,525,594,628,639,697,792] Such studies are stimulated by the enormous use of acetazolamide in the therapy of the glaucomas and by the hope of obtaining agents with fewer systemic side-effects. The availability of such compounds affords the opportunity to explore the correlation of the carbonic anhydrase inhibitory qualities of the agents with their effects upon aqueous secretion.

In man as well as in the experimental animal, maximum doses of the carbonic anhydrase inhibitors acetazolamide (Diamox), ethoxzolamide (Cardrase), methazolamide (Neptazane), and dichlorphenamide (Daranide), produce essentially the same tonographic and aqueous humor chemistry changes.[65] All findings are compatible with some 45% to 55% suppression of aqueous flow in man and a 50% to 60% decrease in rabbits. However, the more potent carbonic anhydrase inhibitors, such as dichlorphenamide or ethoxzolamide, accomplish this degree of secretory suppression at lower milligram dose levels.[68,282,285,318,594] This is also true for the effects of such agents on the renal tubules of mammals as well as alligators.[150,525,628,639] However, with these agents toxicity and side-effects also tend to occur at similarly decreased milligram dose levels. These effects include anorexia, nausea, vomiting, dizziness, and disorientation. Fortunately, some patients who fail to tolerate one of these agents can tolerate others. For this reason ophthalmologists should familiarize themselves with the use of all available carbonic anhydrase inhibitors.

Advertisements quoting reports[594] claiming "twice the potency" for ethoxzolamide (Cardrase) are somewhat misleading, for the effect on intraocular pressure is no greater than that which follows acetazolamide. It merely can be obtained with approximately one-half the milligram dose. In fact, there is evidence that the margin of safety between the effective dose and toxicity of ethoxzolamide is somewhat smaller than that of acetazolamide.[525]

Dichlorphenamide accomplishes maximum secretory suppression in the eye at about one-fifth the dose of acetazolamide. It is also a chloruretic agent, and therefore a part of the systemic acidosis is avoided in the use of this inhibitor.[625] This may be advantageous in some patients, but it also may result in continued renal effects and greater losses of potassium. Care must be taken to follow plasma potassium levels closely in using this agent for prolonged periods.

Methazolamide deserves special mention, for, although it is little more potent than acetazolamide as a carbonic anhydrase inhibitor, it tends to penetrate into the aqueous humor and spinal fluid more readily than does acetazolamide. For this reason doses of this agent may be given which produce less renal effect than conventional doses of acetazolamide but still reduce intraocular pressure in several species and prevent experimental convulsions in mice.[65,296,297] In patients, divided doses of 150 to 300 mg. per day are comparable to 1000 mg. of acetazolamide in ocular effect but similar to 200 to 400 mg. of acetazolamide in renal and systemic electrolyte changes. Therefore, at such dose levels of methazolamide, patients demonstrate much less reduction of plasma bicarbonate and systemic acidosis but still show similar changes in aqueous humor composition and tonographic tracings to that following the larger doses of acetazolamide. In long-term therapy, methazolamide proves useful, especially in those patients who will not tolerate acetazolamide. Unfortunately, central nervous system side-effects of this agent are a major drawback to its continued use in some patients.

Although chlorothiazide (Diuril) is an effective diuretic agent,[60,89,127,486,526,585,668,669,770,784] it is much less active as a carbonic anhydrase inhibitor than the sulfonamides considered above.[125] At diuretic doses, it does not alter aqueous flow appreciably in normal or glaucomatous human eyes, nor does it appear to influence aqueous formation or composition in experimental animals.[65,68,281]

Substitution on the amino nitrogen of effective sulfonamide inhibitors of carbonic anhydrase, such as acetazolamide or methazolamide, results in derivatives that no longer inhibit the enzymes. The administration of these analogs to experimental animals results in no significant alteration in tonographic findings or anterior chamber chemistries.[65] These substituted compounds serve as excellent controls for experimental studies.[483]

It is demonstrated and confirmed in a number of laboratories that most methods applied to date for the study of rate of aqueous flow in experimental animals are consistent with some 50% to 60% suppression of aqueous formation by all effective carbonic anhydrase inhibitors.[65,251-255,300,451,767,806] This includes even such relatively insensitive methods as the turnover of Na^{24}, if posterior chamber, anterior chamber, and plasma concentrations are taken into consideration at enough time intervals.[65] Measurements of only anterior chamber levels at a few time intervals or at steady state may fail to detect such differences, for they may fall within the experimental error.[172,173,231,319,327,433,437,768,778]

Even the reported rise in aqueous humor protein concentration following acetazolamide can be explained by the decrease in rate of flow with more time in the anterior chamber for diffusional exchange. The findings do not require the suggested alteration in permeability of the blood aqueous barrier to protein.[25] Similarly, the rise in anterior chamber aqueous ascorbate concentrations is considered by some observers to be evidence against secretory suppression.[213,415] However, when posterior chamber values are

taken into account it is apparent that the data for rabbits and guinea pigs are compatible with flow rates reduced by about 50% and that the transfer rates of ascorbate into the eye are actually reduced by some 25%.[65]

It is now generally agreed that carbonic anhydrase inhibitors act directly on the enzyme in the ciliary epithelium and decrease the rate of formation of aqueous humor.[178, 415] Additional evidence for this thesis is provided by a study of the action of acetazolamide in the eye of the elasmobranch.[483] In this species there is no carbonic anhydrase in the renal tubule, and thus acetazolamide induces no change in plasma bicarbonate concentrations. Nevertheless, as in the nephrectomized rabbit, guinea pig, or cat, significant decreases in aqueous humor bicarbonate follow acetazolamide administration. As indicated above, the effects of methazolamide in man also provide evidence for a direct effect upon the eye. This drug produces ocular effects of the same magnitude as acetazolamide but in doses which minimize the alteration in renal function and systemic electrolyte concentrations. Recently reported experiments on cats are also very convincing that there is a direct effect upon the eye.[794] The injection of isotonic acetazolamide into one carotid and an inactive sulfonamide derivative into the other results in a more rapid and profound fall in intraocular pressure on the acetazolamide-injected side. Nevertheless, systemic electrolyte changes do occur in the intact animal and may contribute to the ocular effects observed clinically. Some observers even believe that these play a major role.[122,213,234,245] The detailed action of carbonic anhydrase in the formation of aqueous humor awaits more intimate knowledge of the secretory mechanisms involved.

Most secretory processes that are dependent upon carbonic anhydrase involve the formation of a product which differs in hydrogen ion concentration from plasma. Speculation usually attributes a direct role to carbonic anhydrase in supplying hydrogen and/or bicarbonate ions for secretion or ion exchange or an indirect role in maintaining buffering capacity of the secretory site.[20,95,120,126,129,131,132,150,159,170,174,203, 227,242,256,268, 284, 296, 297, 335, 350, 362, 363, 387, 415, 472, 506,509,510,511,582-584,621,663,666,671,672,675,698] At any rate the availability of carbonic anhydrase inhibitors have proved to be of enormous heuristic value in the study of aqueous humor dynamics and of various transport mechanisms in other sites.

3. Other Alterations in Rate of Aqueous Secretion: (*a*) Epinephrine. Additional studies confirm the ability of topical epinephrine bitartrate (4.5%) to reduce the rate of aqueous formation. Of considerable practical significance in the management of the chronic simple and chronic secondary glaucomas treated with miotics is the finding that the secretory effects of this agent are additive to those of acetazolamide.[69] Thus one may induce some 50% suppression of flow by acetazolamide and obtain an additional 30% effect on the residual flow with topical epinephrine, resulting in a total effect of 65% to 70% inhibition of aqueous formation. Similarly, epinephrine alone added to the miotic regimen reduces aqueous secretion by some 35%, and the addition of acetazolamide again induces some 50% further suppression of the residual flow. Clinically, the combined use of miotics, systemic carbonic anhydrase inhibitors, and topical epinephrine bitartrate in chronic glaucoma can maintain intraocular pressure within normal limits and avoid progression of visual field loss for prolonged periods of time. However, it should be reemphasized that topical epinephrine and related agents can induce acute angle closure in eyes with narrow angles.

The mechanism of action of epinephrine in this and other secretory processes remains unknown.[270,317,384,390,430,507,813] Unfortunately it does not appear to alter secretory rate or intraocular pressure in experimental animals such as the rabbit.

(*b*) Other means of decreasing flow. Contrary to a previous report, in the experience of another clinic, pentolinium fails to alter applanation intraocular pressure,

scleral rigidity, or rate of aqueous flow in normal human or rabbit eyes.[724] Severe acidosis lowers the rate of secretion in rabbits and alters aqueous humor chemistries.[43,156,415] Suggestive evidence indicates again that reductions in aqueous formation also follow trauma, general or retrobulbar anesthesia, radiation, ocular inflammation, experimental glaucoma, surgical procedures (cataract extraction, cyclodialysis, cyclodiathermy), reduction of ocular blood supply, and the administration of various toxic agents to animals or man.[17,19,21,41,42,44,47,48,101,103,117,124,180,186,189,195,201,226,232,270,299,320,321,337,352,413,432,450,463,493,518,524,528,529,535,553,567,603,614,616,617,627,659,682-684,714,747,760,761,786,787,795,796,800,809,810,812] In many of these studies, confusion exists between changes in flow rate and alterations in permeability or diffusion characteristics. The fall in chloride content of rabbit anterior chamber aqueous humor following experimental horse serum uveitis is a curious phenomenon.[45] Further studies of other anion concentrations and aqueous humor dynamics in these animals are needed for a satisfactory explanation.

Persistence of the postoperative hypotony after cataract extraction or glaucoma surgery may result in papilledema and even permanent damage to the optic nerve and macula.[756,783] The mechanism and role of hypotony as a consequence of or as a causative factor in retinal detachments provides entertaining speculation.[42,105,278,515,760] The significance of the initial intraocular pressure in the prognosis for surgical reattachment needs evaluation.

(*c*) Attempts to increase the rate of aqueous secretion. Many agents have been studied in attempts to increase the rate of secretion of aqueous humor. Such a drug would provide exciting possibilities for the study of aqueous humor dynamics and possible additional insight into the mechanism of aqueous humor formation. Furthermore, it would offer an important advance as a provocative test in the diagnosis of glaucoma masked by hyposecretion. It might also prove useful in the therapy of hypotony and postoperative flat anterior chambers.

Although occasional enthusiastic reports appear, ascorbate, steroids, oral lysine, exposure to light and dark, histamine, and other agents fail to alter flow rates consistently in most studies.§ [151,196,449,790] One study on normal human volunteers demonstrates a small (1.6 mm. Hg) but significant average increase in intraocular pressure without change in outflow facility following topical prednisolone administration.[449] However, in glaucomatous patients, where smaller changes in flow rate induce larger and more readily measured alterations in intraocular pressure, the systemic or topical administration of cortisone, hydrocortisone, prednisone, or prednisolone, as well as intramuscular corticotropin (ACTH), fail to raise intraocular pressure significantly.‖ The differences noted may stem from effects of steroids limited to the normal eye, alterations in scleral rigidity, or the unorthodox manner of interpreting the tonographic tracings in the study on normal eyes.[449]

III. Episcleral Venous Pressure (P_v)

Relatively few studies of alterations in aqueous and episcleral veins in glaucomatous and normal eyes are published in this year's literature. Conflicting reports continue to appear as to variations in pressure in these vessels with intraocular pressure, with speculation and questions as to cause and effect.[224,312-314,382,395,475,581] As indicated above, variations in the elevation of P_v during tonography may be a major source of error in the evaluation of outflow facility in normal eyes.[277]

Speculation as to an induced decrease in P_v[172,173] rather than a suppression of aqueous formation to account for the pressure-lowering effects of carbonic anhydrase inhibitors is refuted by actual measurements of P_v in rabbit and human eyes. These demonstrate no significant alterations following acetazolamide administration.

§ Tarkkanen, A., and Becker, B.: Unpublished observations, 1957.

‖ Yamasaki, M., and Becker, B.: Unpublished observations, 1955.

IV. Miscellaneous Glaucoma Topics

A. Visual Fields and Optic Nerve.—The vulnerability of the individual optic nerve to damage by a particular intraocular pressure remains one of the most important challenges facing investigators and clinicians concerned with glaucoma diagnosis and management.[30,213,277,278,465,544] Unfortunately, the approach is still largely a retrospective one, and inadequate data are available for even empirical conclusions about the individual eye. Better methods are needed for the study of the effects of given pressure levels on the function of the particular optic nerve. The water-drinking campimetric test and the effects of induced pressures on quantitative perimetry and skiascotometry appear to offer promise along these lines.[277,278,556]

The nutrition and metabolism of the optic nerve must play important roles in the maintenance of its function at given pressure levels. Thus, in addition to more sensitive techniques of visual-field and fundus examinations, interest is expressed in the anatomic relationships and variations of the optic nerve, the nature of the blood supply to the optic nerve and its dependence upon systemtic blood pressure, the nutritional status of the patient, and the metabolic requirements and enzymatic characteristics of the ganglion cells and optic nerve.[111,114,128,130,165,168,192,199,204,235,239,277,278,292,316,330,372,377,378,411,448,464,465,539,544,548,549,575,577,606,612,648,692,748,749,797,798,811,820]

The reported observations of occasional progression of glaucomatous field loss when systemic blood pressure is lowered are of considerable theoretical as well as of practical interest.[334,464] On the other hand, although nerve-fiber-bundle defects may be seen in carotid occlusions, they are not the usual visual-field changes found in this condition. Perhaps this type of defect is not recorded more frequently in carotid occlusions because of anastomoses or possible decreases in rate of aqueous humor formation resulting from the decreased blood supply to the ciliary epithelium.

B. Glaucoma Detection.—Routine surveys continue to reveal a high incidence of undetected glaucoma in the population, especially in persons over the age of 35 to 40 years.[23,31,369,373,466,589,595,630,755,757] Confusion exists in borderline cases, however, on criteria for diagnosis. Although adequate data are available to establish statistical norms for intraocular pressure and outflow facility, the diagnosis in the individual eye often remains questionable until nerve damage occurs. Basic information is needed on the natural life history of chronic simple glaucoma. Frequent errors in tonometric surveys arise from the calibration and limitations of the instruments used, measurements made under less than ideal conditions for the subject and examiner, variations from assumed normal scleral rigidity, and the phenomenon of hyposecretion even in the presence of outflow impairment. The routine use of the applanation tonometer in the office practice of ophthalmologists will serve to detect a large number of patients with unsuspected glaucoma if all eyes with readings greater than 20 mm. Hg are subjected to extensive further evaluation.

The study of members of the families of patients with glaucoma leads to the detection of a number of cases of advanced glaucoma.[364,650,710,711] As indicated above, outflow defects in family populations are even commoner than established glaucoma and may provide excellent opportunities for following the progression of the disease process from its earliest stages.[67]

Unfortunately, such suggested short cuts as the phosphenator have proved unreliable when subjected to careful study and are of no value in glaucoma detection.[322,407,408,455]

The Harrington-Flocks Screener provides a simple device for detection of field defects and is a useful aid in glaucoma case-finding. Although this rapid procedure can only detect glaucoma after damage has taken place, and a number of false positives appear, it does serve as a useful supplement to other methods when inadequate time and personnel are available for visual-field examinations.[406,623]

Additional efforts are directed toward the education of the public, the medical student,

the general practitioner, and even the ophthalmologist as to the existence and detection of glaucoma.[35,139,160,169,197,217,238,344,345,369,371,386,391,423,466,543,588,632,670,712,735,737,755,757,771,772] Routine tonometry must replace tactile evaluation as a part of every eye examination.[495] A high index of suspicion remains the first and most important factor in glaucoma detection.

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News and Comment

SOCIETY NEWS

Scientific Session of Section on Ophthalmology.—The annual session was held in San Francisco from June 24 to 26, 1958. Approximately 400 persons, a record for attendance on the West Coast, were present throughout the meeting. Prof. Gösta Karpe, of Stockholm, Sweden, was the Guest of Honor of the Section.

The following prizes and honors were awarded:

1. The prize medal in ophthalmology was awarded to Peter C. Kronfeld for his many contributions to our specialty.

2. The $250 prize for the best exhibit was awarded to L. K. Garron, M. J. Hogan, W. K. McEwen, and M. L. Feeney for their exhibit, "Electron Microscopy of Ocular Tissue."

3. The $250 prize was awarded to Warren A. Wilson for his paper, "Galactosemia with Associated Cataracts in Children," judged on the basis of presentation and originality.

The following officers were elected: Frank B. Walsh, Chairman; Philip M. Lewis, Vice-Chairman; Henry F. Allen, Assistant Secretary; Ralph O. Rychener, Delegate to House of Delegates; W. Howard Morrison, Alternate Delegate to House of Delegates, and Frank W. Newell, Representative to Scientific Exhibit.

ANNOUNCEMENTS

Meeting of New Orleans Academy of Ophthalmology.—The Ninth Annual meeting of the New Orleans Academy of Ophthalmology will be held in New Orleans, in the Roosevelt Hotel, Feb. 23 to 27, 1959, featuring "Diseases and Surgery of the Retina." The panel will include Drs. Arthur J. Bedell, Harold F. Falls, Bertha A. Klien, Dohrmann K. Pischel, Wilbur C. Rucker, Charles L. Schepens, Donald M. Shafer, and Lorenz E. Zimmerman. The registration fee of $75 includes associate membership in the Academy for the year 1959, as well as all other features of the convention. Hotel reservations should be made early by writing directly to the Executive Secretary, P. O. Box 469, New Orleans.

Books

L'embryologie de l'oeil et sa tératologie. C. Dejian, F. Hervanet, et G. Leplat. Price, not given. Pp. 713, with 534 figures and 10 color plates. Masson & Cie, 120 Blvd. Saint-Germain, Paris, 1958.

This year's publication of the Societé française d' ophthalmologie follows the pattern set in previous monographs. It is an exhaustive review of the present state of knowledge concerning the embryology and teratology of the eye. Much of the text is based upon personal studies by the authors, but an extensive review of the literature is included in each section.

Divergent theories concerning normal and abnormal development are carefully defined and evaluated in the light of past and present knowledge. Particular emphasis is placed upon studies which have led to a better understanding of the various influences upon the mechanism of development. Illustrative photomicrographs are used to advantage to amplify the text, and a series of colored drawings is reproduced following the text.

This should be a valuable contemporary reference work for those interested in normal and abnormal developmental anatomy of the eye.

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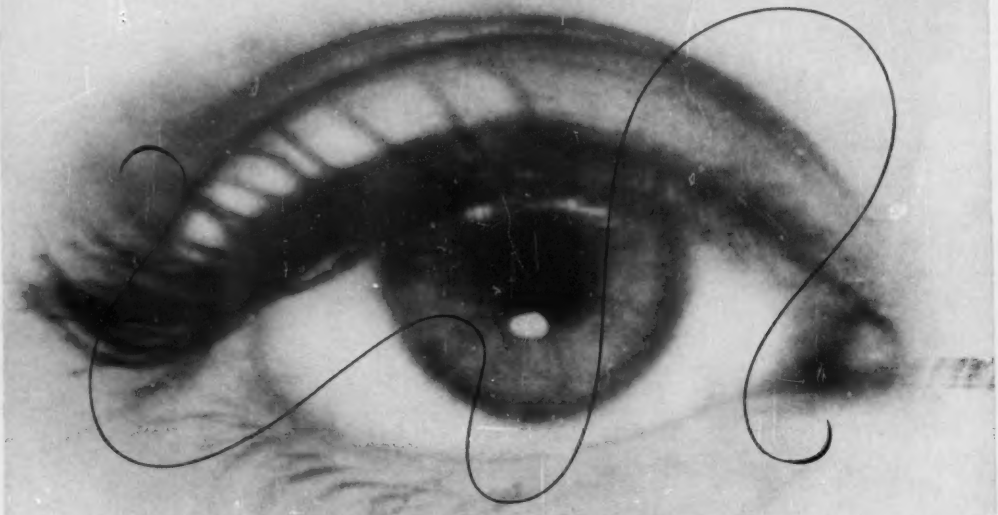

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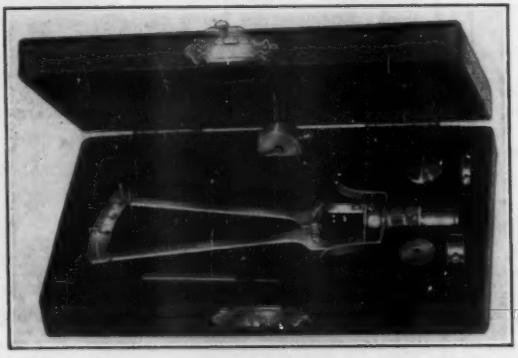

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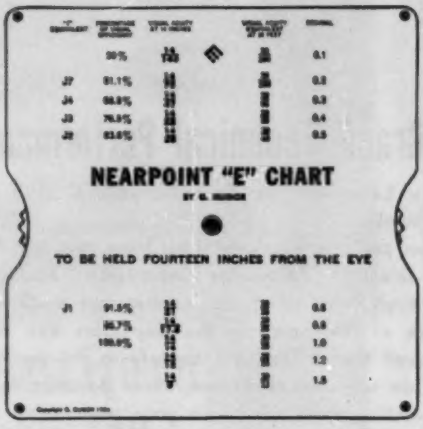

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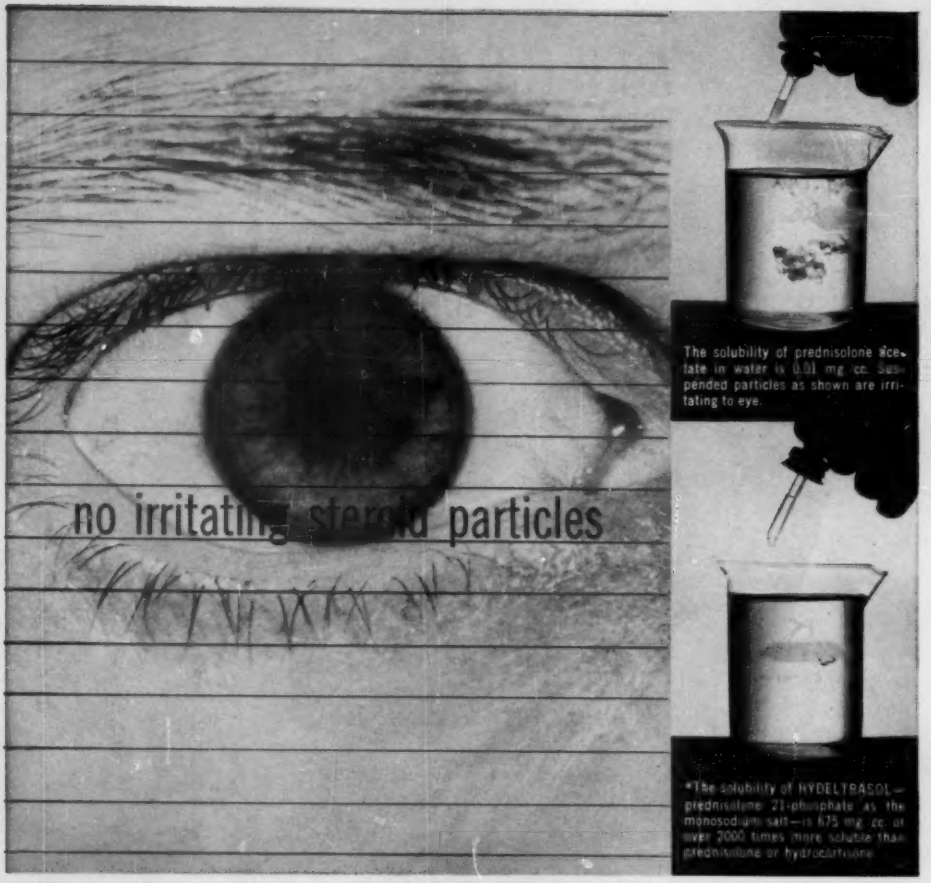
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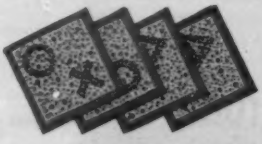

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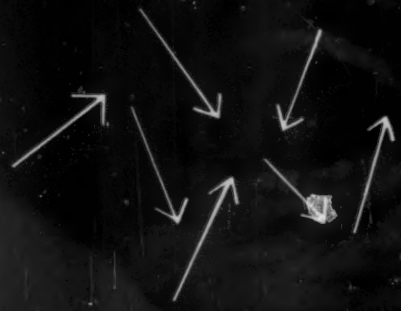

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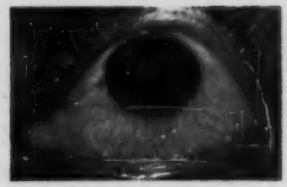

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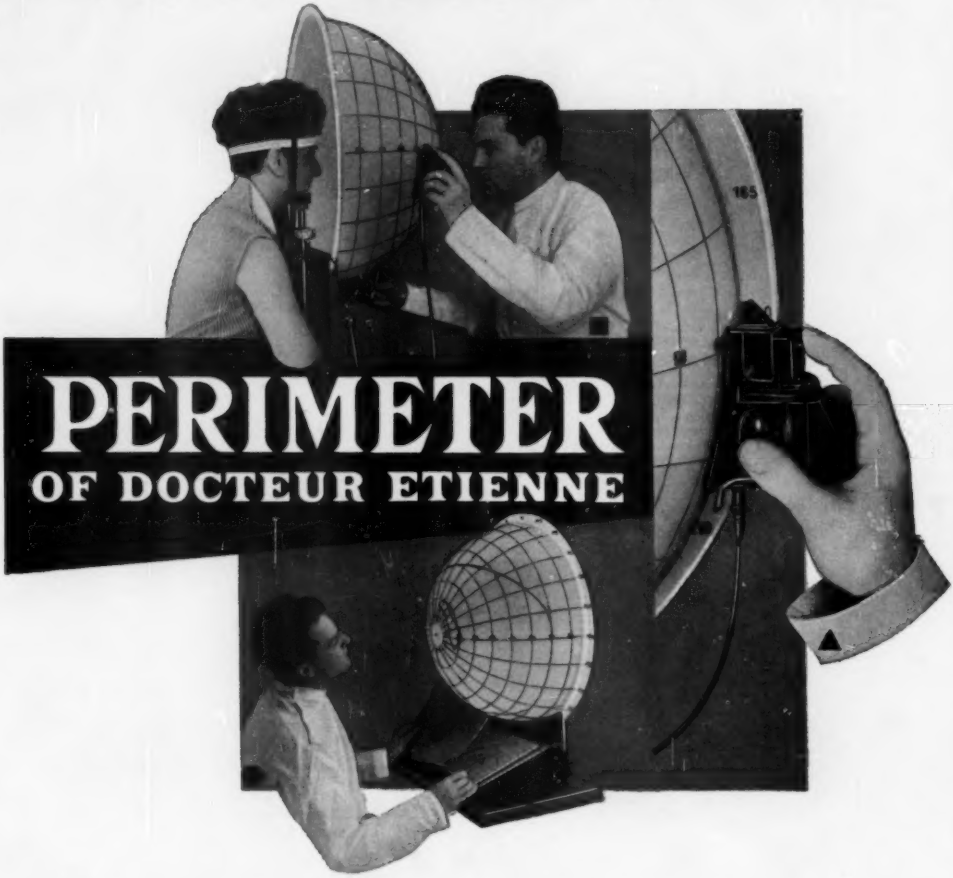

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